23 July 2020
EMA/563387/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/II/0085

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
ARAUC	accumulation ratio of AUC
AST	aspartate transaminase
AUC	area under the concentration versus time curve
AUCτ	AUC during a dosing interval
BA	bioavailability
BL	baseline
BMI	body mass index
BP	blood pressure
bpm	beats per minute
Cavg	average concentration during a dosing interval at steady-state
CF	cystic fibrosis
CFF-TDN	Cystic Fibrosis Foundation Therapeutics Development Network
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RD	Cystic Fibrosis Questionnaire-Revised Respiratory Domain
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CI	confidence interval
CK	creatine kinase
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CSR	clinical study report
CYP	cytochrome P450
C-QTc	concentration-QTc
DBP d	iastolic blood pressure
DDI	drug-drug interaction
ECFS-CTN	European Cystic Fibrosis Society Clinical Trials Network
ECG	electrocardiogram
EE	ethinyl estradiol
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	End-of-Phase 2
E-R	exposure-response
EU	European Union
F/F	homozygous for *F508del*
F/G	heterozygous for *F508del* and a gating mutation
F/MF	heterozygous for *F508del* and an MF mutation
F/RF	heterozygous for *F508del* and a residual function mutation *F508del CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV1	forced expiratory volume in 1 second
G	gating
GCP	Good Clinical Practice

GGT	gamma-glutamyl transferase
HBE	human bronchial epithelial
HR	heart rate
IA	interim analysis
iFAS	interim Full Analysis Set
INR	international normalized ratio
IV	intravenous
IVA	ivacaftor
LFT	liver function test
LN	levonorgestrel
LS	least squares
LUM	lumacaftor
MA-FAS	Meta-analysis Full Analysis Set
MCID	minimum clinically important difference(s)
MF	minimal function
MMRM	mixed-effects model for repeated measures
OATP1B1	organic anion transporting polypeptide B1
OATP1B3	organic anion transporting polypeptide B3
OE	ophthalmological examination
OLE	open-label extension
OL-FAS	Open-label Full Analysis Set
PD	pharmacodynamic
PDCO	European Medicines Agency Pediatric Committee
PEx	pulmonary exacerbation
P-gp	P-glycoprotein
PIP	pediatric investigation plan
PK	pharmacokinetic
PMR	post-marketing requirement
popPK	population PK
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
PY	patient-year
q12h	every 12 hours
qd	once daily
qod	every other day
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RF	residual function
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SwCl	sweat chloride
t½	terminal phase half-life
TC	triple combination
TEAEs	treatment-emergent adverse events
TEZ	tezacaftor
tmax	time of maximum concentration
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (Ireland) Limited submitted to the European Medicines Agency on 7 April 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the combination regimen of the ivacaftor 150 mg tablets with elexacaftor/tezacaftor/ivacaftor fixed dose combination (FDC) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis who have at least one *F508del* mutation in the *CFTR* gene; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.8 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Kalydeco, was designated as an orphan medicinal product EU/3/08/556 on 8 July 2008. Kalydeco was designated as an orphan medicinal product in the following indication: treatment of cystic fibrosis (CF).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0163/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0163/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	7 April 2020
Start of procedure:	25 April 2020
PRAC Rapporteur Assessment Report	25 June 2020
CHMP Rapporteur Assessment Report	1 July 2020
PRAC members comments	01 July 2020
PRAC Outcome	9 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 July 2020
CHMP similarity assessment report adopted on	23 July 2020
CHMP Opinion	23 July 2020

2. Scientific discussion

2.1. Introduction

A marketing authorisation application (MAA) for a fixed dose combination (FDC) film-coated tablet of elexacaftor (VX-445) 100 mg/tezacaftor (VX-661) 50 mg/ivacaftor (VX-770) 75 mg (EMEA/H/C/005269) has received positive opinion from the CHMP, in June 2020, for the treatment of cystic fibrosis (CF) in patients 12 years of age and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or heterozygous for the *F508del* in the *CFTR* gene with a minimal function (MF) mutation.

This type II variation application has been submitted to include the use of Kalydeco in combination with Kaftrio. Of note, this application was submitted before the approval of Kaftrio, thus, the initially proposed indication for Kalydeco in association with Kaftrio does not correspond to the agreed indication of Kaftrio.

The daily dosing regimen consists of oral administration of 2 elexacaftor/tezacaftor/ivacaftor FDC tablets in the morning and 1 ivacaftor (150 mg) tablet (Kalydeco) in the evening.

2.1.1. Problem statement

Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. CF is caused by mutations in the *CFTR* gene that result in absent or deficient function of the *CFTR* protein at the cell surface. The *CFTR* protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water

absorption and secretion. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF.

In people with CF, loss of chloride transport due to defects in the *CFTR* protein result in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF.

The biochemical defect of defective chloride channel function is present from birth, with the sequelae of lung, pancreatic and other organ involvement emerging progressively throughout childhood and into adulthood.

F508del is the most common disease-causing mutation, and the vast majority of CF patients (~84.7% in the US and ~81.1% in Europe) have this mutation on at least 1 allele.

Epidemiology

CF affects approximately a total of 31,000 individuals in the US and a total of 42.000 in the EU (excluding the data from Russia, Turkey and Israel)[1,2]. The incidence and prevalence of CF varies between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations. In Europe, the median age of all CF patients is 18.5 years (with youngest patient being diagnosed just after birth and the oldest patients being 88.4 years of age). Despite advances in treatment, the current median age of death in a patient with CF was approximately 31 years in 2018, and the future predicted median age of survival is approximately 47 years[1,2].

Biologic features

CF is an autosomal recessive disease in which disease-causing mutations are present on both *CFTR* alleles that make up a patient's genotype. Severity of CF is determined by the extent of the loss of *CFTR*-mediated chloride transport caused by the 2 *CFTR* mutant alleles. Historically, these *CFTR* mutations have been categorized in different ways including a class system based on their effect on *CFTR* protein synthesis or function (Classes I through VI) and grouping based on phenotypic expression (e.g., residual *CFTR* function). To study the impact of *CFTR* modulators, Vertex has categorized mutations as follows: gating (G), residual function (RF), and minimal function (MF).

Patients with CF who have 2 alleles that result in complete or near complete loss of *CFTR*-mediated chloride transport (e.g., *F508del*, Class I mutations which make no *CFTR* protein, gating mutations such as *G551D*) demonstrate severe CF characterized by early onset and relatively rapid disease progression, with sweat chloride concentrations (an in vivo marker of *CFTR* function) typically greater than 90 mmol/L. For patients with residual function mutations or those who are partially treated by existing *CFTR* modulator therapy, further increases in *CFTR*-mediated chloride transport are expected to be associated with further normalization of physiology and disease consequences.

Clinical presentation and diagnosis

CFTR is an ion channel that regulates the flow of chloride and other ions across epithelia in various tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands. Decreased CFTR quantity or function results in the failure to regulate chloride transport in these tissues leading to the multisystem pathology associated with CF. Progressive loss of lung function is the leading cause of mortality. The clinical manifestations are those of progressive airway obstruction and bronchiectasis,

with periods of worsening pulmonary symptoms associated with a decline in pulmonary function and increased bacterial density in airway secretions (pulmonary exacerbations). Obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs, leading to respiratory failure. In addition, poor growth and nutritional status have historically been common in patients with CF owing to a number of factors, including pancreatic insufficiency-related fat malabsorption, increased energy expenditure attributable to progressive lung disease, appetite suppression attributable to chronic infection, and CF-related diabetes.

Management

The approved *CFTR* modulators (IVA, LUM/IVA, and TEZ/IVA) were developed in specific subsets of CF patients, grouped by specific *CFTR* mutations and genotypes that were responsive to each of the modulators. This approach led to the approval of *CFTR* modulator regimens based on multiple individual mutations and genotypes: e.g., gating mutations, residual function mutations, patients homozygous for *F508del* (Table 1).

Table 1 Indications for CFTR Approved Modulators in the EU

CFTR Modulator	Approved Genotype
Ivacaftor (IVA; Kalydeco™)	CF patients 6 months of age and older and weighing 5 kg or more who have 1 of the following gating (Class III) mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*. CF patients 18 years of age and older who have an *R117H* mutation in the *CFTR* gene.
Lumacaftor/ivacaftor (LUM/IVA; Orkambi™)	CF patients 2 years of age and older who are homozygous for *F508del* (F/F genotype).
Tezacaftor/ivacaftor (TEZ/IVA; Symkevi™ + Kalydeco)	CF patients 12 years of age and older who are homozygous for *F508del* or who are heterozygous for the *F508del* mutation and have 1 of the following mutations in the *CFTR* gene: *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272-26A→G*, and *3849+10kbC→T* (F/F and F/RF genotypes).

CF: cystic fibrosis; F/F: *F508del* on both alleles; F/RF: heterozygous for *F508del* and a residual function mutation; IVA: ivacaftor; LUM: lumacaftor; TEZ: tezacaftor

Kaftrio is a triple combination product which contains the new *CFTR* modulator elexacaftor (VX-445), and the known *CFTR* modulators ivacaftor and tezacaftor; Kaftrio received a positive opinion from CHMP in July 2020.

2.1.2. About the product

In the EU, Kalydeco tablets are indicated for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with CF who have an R117H CFTR mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*. Kalydeco tablets are indicated as well in a combination regimen with tezacaftor 100 mg/ivacaftor 150 mg tablets for the treatment of adults and adolescents aged 12 years and older with CF who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T*.

Kaftrio, a fixed dose combination (FDC) film-coated tablet of elexacaftor (VX-445) 100 mg/tezacaftor (VX-661) 50 mg/ivacaftor (VX-770) 75 mg (EMEA/H/C/005269) received positive opinion from the CHMP in July 2020 for the following indication:

"Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation (see section 5.1)."

This extension of application is submitted to include the use in combination with Kaftrio as per the following approved posology:

- Morning dose: 2 fixed-dose combinations (FDC) tablets of Kaftrio (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg).
- Evening dose: 1 tablet containing 150 mg of Kalydeco (ivacaftor).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The VX-445/TEZ/IVA development program consisted of 10 clinical studies, including a Phase 3 program enrolling over 500 CF subjects providing approximately 330 patient-years of exposure.

In January 2018, Vertex received Scientific Advice from the CHMP (EMA/CHMP/SAWP/9006/2018) on the proposed clinical development programme for Kaftrio in combination with ivacaftor.

The Protocol Assistance pertained to the following clinical aspects:

- Adequacy of the proposed clinical development plan to support an initial marketing authorisation application (MAA) for Kaftrio in CF patients aged 12 and older heterozygous for the *F508del* mutation and a "MF" mutation, including a single 24-week pivotal randomized, double-blind, placebo-controlled Phase 3 study in approximately 360 F/MF subjects with the primary endpoint absolute change in ppFEV1 at Week 4. The study would also assess the effect on pulmonary exacerbation rate. Specific questions were raised on the use of an interim analysis of the 4-week primary endpoint to support the MAA submission, and the proposed safety database.
- Acceptability of the proposed clinical development plan to support indication to patients with CF aged 12 years and older who have the *F508del* mutation on at least 1 allele, including a randomized, double-blind, active comparator-controlled (TEZ/IVA), 4-week Phase 3 study in CF subjects, aged 12 years and older, with the F/F genotype with the primary endpoint absolute change in ppFEV1 at Week 4.

2.2. Non-clinical aspects

2.2.1. Introduction

This is an application for the combined use of ivacaftor (as an evening dose) with Kaftrio.

The MAH provided non-clinical studies conducted to support the approval of Kaftrio. Since Kalydeco is already authorised and its non-clinical profile is known, the main part of the information in this section refers to the relevant results on the use of Kalydeco in combination with Kaftrio.

Elexacaftor (VX-445), a component of the fixed-dose combination Kaftrio, is a novel CFTR corrector that has both a different chemical structure and a different mechanism of action from first-generation CFTR correctors, like tezacaftor.

No additional non-clinical data are submitted for this extension of indication for Kalydeco. This is

considered acceptable.

2.2.2. Pharmacology

There is no validated animal model for CF that fully mimics the human multi organ affected disease. Furthermore, the proposed treatment is specific for mutated CFTR proteins.

CFTR modulators are small molecules that target specific defects caused by mutations in the *CFTR* gene. Correctors (tezacaftor and lumacaftor) facilitate the cellular processing and trafficking of *CFTR* to increase the quantity of *CFTR* at the cell surface. Potentiators (ivacaftor) increase the channel open probability (channel gating activity) of the *CFTR* protein delivered to the cell surface to enhance chloride transport. A combination of a corrector and a potentiator, should results in sufficient levels of *CFTR* at the surface, which is then enhanced for its gating function. A summary of selected pharmacodynamic studies of the different modulators, based on the Kaftrio application is provided below.

Primary pharmacodynamic studies

Binding of elexacaftor and tezacaftor to CFTR protein was measured using thermostabilized CFTR (TS-CFTR) reconstituted into nanodiscs. The results show that both molecules bind to different, non-competing binding sites on TS-CFTR. Elexacaftor binds to both MSD1 and MSD2, which is different to tezacaftor, which binds to MSD1 only.

The MAH used two groups of HBE cells to study the effect of elexacaftor on top of tezacaftor and or ivacaftor on the processing and trafficking of F508del-CFTR. One group consisted of HBE cells from three different donors all harbouring two *F508del* alleles (F/F group). The other group consisted of HBE cells from four donors, all harbouring one *F508del* allele and one allele with a minimal function (MF) mutation (F/MF group). Among these four F/MF donors; two donors harbour a *G542X* mutation, one donor harbours a *3905insT* mutation and one donor harbours an *E585X* mutation.

The results showed that elexacaftor incubation of the cells results in an increase of glycosylated *CFTR* compared to untreated, tezacaftor treated and ivacaftor treated cells. Treatment with tezacaftor and elexacaftor resulted in a synergistic effect. This effect seems to be dampened by the co-incubation with ivacaftor, but the potentiator ivacaftor is very likely needed to improve the function of the channels that have reached the membrane. Overall, the incubation with the combination of the three active compounds resulted in a higher increase in glycosylated mutant *CFTR* as compared to incubation with one corrector and one potentiator, thus with tezacaftor and ivacaftor or elexacaftor and ivacaftor.

In addition to the effect on the processing, the effect on chloride transport of elexacaftor alone or in combination with tezacaftor and or ivacaftor was tested in F/F HBE cells or F/MF HBE cells by Using chamber electrophysiology. The results of this chloride transport assay showed better results for the triple combination. In addition, the effect of VX-445 alone and in combination with tezacaftor, with and without ivacaftor, on channel gating activity was determined using patch clamp experiments. After spiking with the corrector(s) alone, channel opening was only very minimal. After spiking with the corrector(s) and the potentiator channel opening was achieved efficiently, supporting the use of ivacaftor in the triple combination.

Secondary pharmacodynamic studies

The secondary pharmacodynamics of tezacaftor, ivacaftor, and M6-IVA (a major metabolite of ivacaftor) were previously established in the support of the registration of Kalydeco, Orkambi, and Symkevi. These data showed that these tezacaftor, ivacaftor, and M6-IVA had a low propensity to elicit off-target effects

at therapeutic exposures. In addition, elexacaftor seems to be selective for CFTR, and have minimal off target effects.

Pharmacodynamic drug interactions

No dedicated pharmacodynamics drug interaction studies were submitted. The pharmacodynamic interaction of the elexacaftor, tezacaftor and ivacaftor was assessed in the *in vitro* primary pharmacodynamic studies. Ivacaftor may interfere slightly with the increase of mature *CFTR* levels due to tezacaftor and elexacaftor incubation, however this would have minimal impact and is acceptable considering the need to add ivacaftor in order to open the chloride channels.

Safety pharmacology programme

Results from the conventional studies on safety pharmacology suggested a low potential for elexacaftor, tezacaftor or ivacaftor to elicit effects on CNS, respiratory or cardiovascular parameters at clinically relevant exposures.

2.2.3. Pharmacokinetics

The non-clinical pharmacokinetics (PK) of VX-445 were investigated in a series of *in vitro* and *in vivo* studies as part of Kaftrio application. The PK properties of tezacaftor, ivacaftor and the combination tezacaftor/ivacaftor were previously assessed in the registration programs for Symkevi and Kalydeco. No additional PK data for Kalydeco are available which is considered acceptable for this application. No dedicated non-clinical PK DDI studies have been submitted.

2.2.4. Toxicology

An extensive non-clinical package was submitted to evaluate the safety of VX-445 as part of Kaftrio application. No additional toxicology data on the use of Kalydeco with Kaftrio were submitted. This was considered acceptable by CHMP.

Combination repeat-dose toxicity studies to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions. The potential for synergistic toxicity on male reproduction has not been assessed.

2.2.5. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): VX-770 **CAS-number:** 873054-44-5					
PBT screening		**Result**			**Conclusion**
Bioaccumulation potential –log Kow		➢ 4.75 at pH 7			Potential PBT YES
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Persistence	DT_{50}	$DT_{50, system}$ = 1233/261 d (sandy silt loam sediment / sand sediment). DT_{50} soil = 166 to 316 days			Soil DT_{50} values corrected to 12°C Conclusion: vP
Bioaccumulation	BCF	<2000			Not B
Toxicity	NOEC (aquatic)				
PBT-statement					
Phase I					
Calculation	**Value**	**Unit**			**Remarks**
$PEC_{surfacewater}$ Refined	0.026	0.081 µg/L			>0.01 threshold Yes
Other concerns (e.g. chemical class)					None
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =11800 (sewage sludge) K_{oc} = 10800 (sewage sludge) K_{oc} = 3710 (sandy loam) K_{oc} = 1970 (sandy clay loam) K_{oc} = 5900 (clay loam)			Terrestrial studies triggered
Ready Biodegradability Test	OECD 301	Not conducted			Considered not ready biodegradable
Aerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} water = 4.4 and 1.7 days DT_{50} sediment = 581 and 123 days % shifting to sediment (99 days) =78 % and 50.3% (VX-770); 96.3 % and 96.5% (total radioactivity)			No decline rate in the sediment phase could be calculated.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition *(Pseudokirchnerilla subcapita)*	OECD 201	NOEC	54.7	µg/L	Growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.1	µg/L	
Fish, Early Life Stage Toxicity *(Pimephales promelas)*	OECD 210	NOEC	29	µg/L	
Activated Sludge, Respiration Test	OECD 209	NOEC	1 x 10^6	µg/L	

Phase IIb Studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Units**	**Remarks**
Bioaccumulation	OECD 305	BCF	<2000		Not B
Aerobic Transformation in Soil (Four soils)	OECD 307	DT_{50} 166 to 316 days (DFOP model)			Combined VX-770 and M2 at 12°C
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	Effect			Not possible to estimate. It could be anticipated no effect at 100 x PECsoil
Terrestrial Plants, Growth (Six species)	OECD 208	NOEC	1000	mg/kg dw	Cabbage, carrot, lettuce, tomato, oat, and onion
Earthworm, Acute Toxicity Test	OECD 207	NOEC	1000	mg/kg dw	
Collembola, Reproduction Test	OECD 232	NOEC	1000	mg/kg dw	
Sediment dwelling organism (*Chironomus riparius*)	OECD 218	NOEC	7463	mg/kg dw	Corrected for 10% organic carbon

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of ivacaftor.

2.2.6. Discussion on non-clinical aspects

This type II variation is submitted to include the combination of ivacaftor with Kaftrio.

Pharmacological studies performed for the Kaftrio non-clinical application showed that VX-445 and TEZ bind to CFTR simultaneously at different binding sites.

Furthermore, VX-445 incubation of the cells resulted in an increase of glycosylated *CFTR* compared to non-treated, TEZ treated and IVA treated cells. Treatment with TEZ and VX-445 resulted in a synergistic additive effect on mature fraction of CTFR. However, the effect was reduced by the addition of IVA. Upon request by CHMP, the MAH clarified that the mechanism causing the small reduction in mature CFTR by IVA is not known. According to Veit et al., a plausible explanation would be that IVA interacts with F508del-CFTR to cause conformational destabilization. Veit et al., suggest that "the negative effect of VX-770 (IVA) would be more pronounced in patients having a single copy of F508del-CFTR", which is not consistent with the MAH observations. Therefore, even with the small reduction in mature CFTR, IVA is required to restore the defective channel gating activity of the F508del-CFTR delivered to the cell surface by VX-445/TEZ.

Ivacaftor is associated with a decrease of overall fertility index and number of pregnancies in females; and the VX-445 component of Kaftrio with reduced fertility and male reproductive organs toxicity. Thus, the potential for synergistic toxicity on male reproduction cannot be ruled out.

2.2.7. Conclusion on the non-clinical aspects

Based on the non-clinical package submitted for Kaftrio and on the already known non-clinical profile of Kalydeco, the use of Kalydeco in combination with Kaftrio is considered acceptable from a non-clinical point of view.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2 Overview of Study Designs of VX-445 Phase 3 Studies

Study Identifier	Study Design and Type of Control	Study Centers	Key Inclusion Criteria	Treatment	Number of Subjects Assessed for Efficacy (FAS; OL-FAS)/ Completed Treatment	Duration of Treatment Study Status	Efficacy Endpoints
Phase 3 Controlled Studies							
VX17-445-102	Randomized, placebo-controlled, double-blind, 2-arm, parallel-group	110 sites in North America, Europe, and Australia	Confirmed diagnosis of CF, F/MF genotype, ≥12 years of age, ppFEV$_1$ ≥40 and ≤90	VX-445 200 mg qd + TEZ 100 mg qd/ IVA 150 mg q12h Placebo (Randomized 1:1)	VX-445/ TEZ/IVA: 200/197 Placebo: 203/203	24 weeks Completed	**Primary Endpoint** • Global protocol: Absolute change from baseline in ppFEV$_1$ at Week 4 • European protocol: Absolute change from baseline in ppFEV$_1$ through Week 24 **Key Secondary Endpoints** • Global protocol: Absolute change from baseline in ppFEV$_1$ through Week 24 • European protocol: Absolute change from baseline in ppFEV$_1$ at Week 4 Global and European Protocols • Number of PEx through Week 24 • Absolute change from baseline in SwCl through Week 24 • Absolute change from baseline in CFQ-R RD score through Week 24 • Absolute change from baseline in BMI at Week 24 • Absolute change from baseline in SwCl at Week 4 • Absolute change from baseline in CFQ-R RD score at Week 4 **Other Secondary Endpoints** • Time-to-first PEx through Week 24 • Absolute change from baseline in BMI z-score at Week 24 • Absolute change from baseline in body weight at Week 24 **Additional Endpoints** • Absolute change from baseline in CFQ-R non-RD scores through Week 24 • Absolute change from baseline in TSQM domains at Week 24 (subjects ≥12 to <18 years of age) • Changes from baseline in inflammatory mediators at Week 24 • Changes from baseline in microbiology analysis at Week 24

VX17-445-103	Randomized, active-controlled, double-blind, 2-arm, parallel-group	44 sites in North America and Europe	Confirmed diagnosis of CF, F/F genotype, ≥12 years of age, ppFEV$_1$ ≥40 and ≤90	VX-445 200 mg qd + TEZ 100 mg qd/ IVA 150 mg q12h TEZ 100 mg qd/ IVA 150 mg q12h (Randomized 1:1)	VX-445/ TEZ/IVA: 55/55 TEZ/IVA: 52/52	4 weeks Completed	**Primary Endpoint** • Absolute change from baseline in ppFEV$_1$ at Week 4 **Key Secondary Endpoints** • Absolute change from baseline in SwCl at Week 4 • Absolute change from baseline in CFQ-R RD score at Week 4 **Additional Endpoints** • Absolute change from baseline in CFQ-R non-RD score at Week 4 • Absolute change from baseline in TSQM domains at Week 4 (only for subjects ≥12 to <18 years of age)
Phase 3 Uncontrolled Study							
VX17-445-105	Open-label extension study	110 sites in North America, Europe, and Australia	Completed study treatment in Study 102 or 103	VX-445 200 mg qd + TEZ 100 mg qd/ IVA 150 mg q12h	VX-445/ TEZ/IVA: 107/0 (subjects from Study 103)	96 weeks Ongoing; data included herein is from IA performed after all subjects from Study 103 completed the Week 24 Visit in Study 105.	**Secondary Endpoints** • Absolute change from baseline in ppFEV$_1$ • Number of PEx • Absolute change in SwCl • Absolute change from baseline in CFQ-R RD score • Absolute change in BMI • Time-to-first PEx • Absolute change in BMI z-score • Absolute change in body weight **Additional Endpoints** • Absolute change in CFQ-R non-RD scores • Changes in inflammatory mediators • Changes in microbiology analysis • Rate of change in ppFEV$_1$

AEs: adverse events; BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; OL: open label; PEx: pulmonary exacerbation; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; qd: once daily; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor; TSQM: Treatment Satisfaction Questionnaire for Medication

2.3.2. Pharmacokinetics

The PK of Kalydeco is adequately characterised since authorisation. Within this application the documentation submitted was the PK data package submitted for Kaftrio application, which was considered adequate.

No additional data are needed to support this application for combination regimen with Kaftrio.

2.3.3. Pharmacodynamics

The pharmacodynamics of Kalydeco and Kaftrio has been adequately characterised. No new data are required in support of this application.

2.3.4. Discussion on clinical pharmacology

The clinical pharmacology of IVA and IVA/TEZ/VX-445 has been adequately investigated.

Nevertheless, regarding the dose advice for CF patients with hepatic impairment, although it appears reasonable and can at this stage be accepted for those patients with moderate hepatic impairment, no information has been provided by the MAH on the effect of the proposed dose-reduction on the exposure to the active metabolite M1-TEZ. The MAH has committed to provide such analysis and subsequently re-discuss/refine the dose-advice in moderate hepatically impaired patients. This discussion will be provided at the time that the CSR from Study 007 is submitted as post-approval commitment for Kaftrio.

The agreed posology by CHMP for the use of Kalydeco in combination with Kaftrio has been correctly reflected in the SmPC.

No additional data are required in support of this application.

2.3.5. Conclusions on clinical pharmacology

Overall, VX-445, as well as tezacaftor and ivacaftor pharmacokinetics and pharmacodynamics have been adequately investigated and correctly reflected in the SmPC.

To support the dose advice in patients with hepatic impairment, the MAH committed to submit the final clinical study report of study 007 as a post-approval commitment for Kaftrio by end of Q3 2020. The MAH is also expected to re-discuss/re fine the dose-advice in moderately hepatic impaired patients, taking into account the expected exposure of the active M1-TEZ metabolite. This information is important in support of the dose advice in patients with hepatic impairment.

2.4. Clinical efficacy

A clinical program for Kaftrio Iniital Marketing Authorisation was designed to assess whether the presence of a single F508del allele would be sufficient for CF patients to benefit from the TC regimen.

The core efficacy data are from 2 controlled Phase 3 studies:

- Study **102**: a 24-week study in subjects with a single F508del allele (F/MF)
- Study **103**: a 4-week study in subjects with two F508del alleles (F/F)

Supportive efficacy data are from:

- Phase 1/2 Study **001** in F/MF (Part D) and F/F subjects (Part E)
- Study **105**, an ongoing open-label extension (OLE) study evaluating long-term safety and efficacy for 96 weeks in subjects who participated in Studies 102 and 103.

Additionally, results of a cross study comparison using data from Studies 103 and 105 and Phase 3 studies of TEZ/IVA (Symkevi) which was requested by European Medicines Agency Paediatric Committee (PDCO) provide supportive efficacy data. This comparison is also referred to as the **Meta-analysis** (paediatric investigation plan [PIP] Study C9).

Treatments

Kalydeco was administered as an evening dose in combination with Kaftrio for the phase 3 clinical studies and its extension which is acceptable.

The treatment regimens used in the Phase 3 studies are summarized in Table 3.

Table 3 Summary of Treatment Regimens in VX-445 Phase 3 Studies

	VX-445/TEZ/IVA Arm			
Study Identifier	**VX-445 Dose**	**TEZ Dose**	**IVA Dose**	**Control**
Study 102	200 mg qd	100 mg qd	150 mg q12h	Placebo
Study 103	200 mg qd	100 mg qd	150 mg q12h	TEZ/IVA[a]

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TC: triple combination; TEZ: tezacaftor

[a]The TEZ/IVA dosages for the control group were the same as those used in the TC regimen (the commercial doses of TEZ and IVA).

2.4.1. Dose response studies

Data provided by the MAH was identical to the data package submitted within Kaftrio application. These data supported dose responses related to the mono-components of the fixed-dose combination of Kaftrio and are not described in this procedure.

2.4.2. Main studies

Two main studies were presented within Kaftrio application and have therefore been considered for this application:

Study VX17-445-102:
A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (**F/MF**).

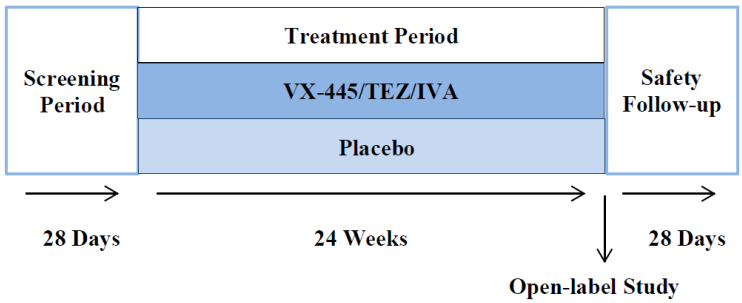
Study VX17-445-103:
A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Homozygous for the *F508del* Mutation (**F/F**).

Methods

Study 102

Subjects with F/MF genotypes were randomized (1:1) to either VX-445/TEZ/IVA or placebo (Figure 1). Randomization was stratified by percent predicted forced expiratory volume in 1 second (ppFEV1) determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 versus ≥18 years of age), and sex (male versus female).

Figure 1 Schematic of Study Design for Study 102

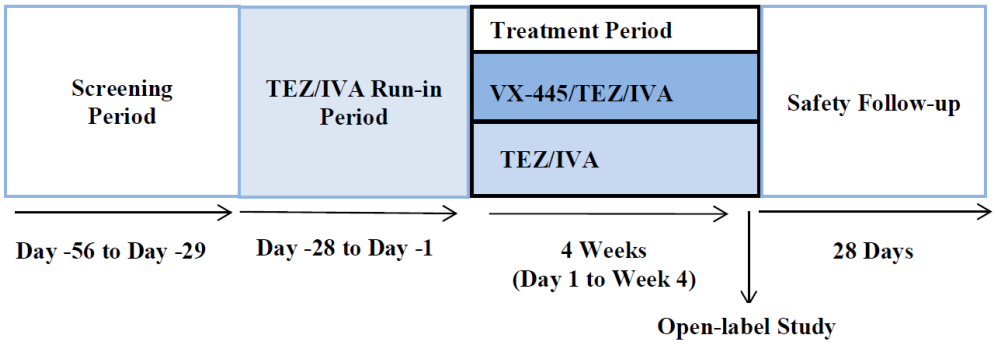


IA: interim analysis; IVA: ivacaftor; TEZ: tezacaftor
Notes: The figure is not drawn to scale. An IA was planned after at least 140 subjects completed the Week 4 Visit and at least 100 subjects completed the Week 12 Visit.

Study 103

After a 4-week TEZ/IVA Run-in Period to establish an on-treatment (TEZ/IVA) baseline for comparison with the Treatment Period, subjects with the F/F genotype were randomized (1:1) to either VX-445/TEZ/IVA or TEZ/IVA (Figure 2). Randomization was stratified by ppFEV1 determined during the TEZ/IVA Run-in Period (<70 versus ≥70) and by age (<18 versus ≥18 years of age) at screening.

Figure 2 Schematic of Study Design for Study 103



IVA: ivacaftor; TEZ: tezacaftor

Study participants

The key *inclusion criteria* were in both studies, aged 12 years and older, FEV1 value ≥40% and ≤90% of predicted mean for age, sex, and height, a confirmed diagnosis of CF by the investigator and stable CF disease as judged by the investigator.

Study **102** included patients heterozygous for *F508del* and an MF mutation (**F/MF**). The eligible MF mutations were pre-specified (see Table 8). Previous clinical studies of TEZ/IVA and LUM/IVA in F/MF patients have failed to demonstrate efficacy.

MF mutations on that list were determined by the MAH to qualify as an MF mutation if meeting one of the following 2 criteria:

(1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein), ***or***

(2) in vitro testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA, ***and*** *evidence of clinical severity on a population basis (as reported in large patient registries).*

Study **103** included patients homozygous for *F508del* (**F/F**). Although currently approved CFTR modulator therapies are available for F/F patients, these patients continue to have progressive lung disease.

The main *exclusion criteria* were similar in both trials, being:

1. Any of the following abnormal laboratory values at screening:
    a. Hemoglobin <10 g/dL
    b. Total bilirubin ≥2 × upper limit of normal (ULN)
    c. Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
    d. Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m2 (calculated by the Modification of Diet in Renal Disease Study Equation) for subjects ≥18 years of age and ≤45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation) for subjects aged 12 to 17 years (inclusive)
2. An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug (Day 1 [Study 102]), or before the first dose of TEZ/IVA in the Run-in Period (Day -28 [Study 103])..

3. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia, Burkholderia dolosa,* and *Mycobacterium abscessus*). For subjects who had a history of a positive culture, the investigator applied the following criteria to establish whether the subject was free of infection with such organisms:

    a. The subject did not have a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.

    b. The subject had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.

Treatments

The treatment regimens used in the Phase 3 studies are summarized below.

Summary of Treatment Regimens in VX-445 Phase 3 Studies

	VX-445/TEZ/IVA Arm			
Study Identifier	**VX-445 Dose**	**TEZ Dose**	**IVA Dose**	**Control**
Study 102	200 mg qd	100 mg qd	150 mg q12h	Placebo
Study 103	200 mg qd	100 mg qd	150 mg q12h	TEZ/IVA[a]

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TC: triple combination; TEZ: tezacaftor

[a] The TEZ/IVA dosages for the control group were the same as those used in the TC regimen (the commercial doses of TEZ and IVA).

Study drug was taken within 30 minutes of the start of a fat-containing meal or snack, such as a standard "CF" meal or snack or a standard meal.

For both studies use of any other CFTR modulator therapy for the study duration was not permitted. For **Study 102** use of CFTR modulators needed to be stopped at least 28 days before the first dose of study drug on Day 1. For **Study 103** patients taking Vertex CFTR modulators right up to the time of screening could be recruited, and they only needed to stop these at the start of the TEZ/IVA run-in period. Those on non-Vertex CFTR modulators had to have a wash out period pre-screening.

Outcomes/endpoints

The primary and secondary efficacy and pharmacodynamic (PD) endpoints evaluated in Studies 102 and 103 are provided in Table 4.

In Study 102, the primary endpoint in the global protocol was absolute change from baseline in $ppFEV_1$ at Week 4. Subsequently, European regulators requested a primary endpoint of absolute change from baseline in $ppFEV_1$ through Week 24, thus a Europe-specific protocol amendment was made to accommodate the request. The global protocol was followed in all regions except Europe.

Table 4 Studies 102 and 103: Primary and Secondary Efficacy and PD Endpoints

	Study 102 (F/MF)	Study 103 (F/F)
Primary endpoint	• Global protocol: Absolute change from baseline in $ppFEV_1$ at Week 4 • European protocol: Absolute change from baseline in $ppFEV_1$ through Week 24	Absolute change from baseline in $ppFEV_1$ at Week 4
Key secondary endpoints	• Global protocol: Absolute change from baseline in $ppFEV_1$ through Week 24 • European protocol: Absolute change from baseline in $ppFEV_1$ at Week 4 Global and European Protocols • Number of PEx through Week 24 • Absolute change from baseline in SwCl through Week 24 • Absolute change from baseline in CFQ-R RD score through Week 24 • Absolute change from baseline in BMI at Week 24 • Absolute change from baseline in SwCl at Week 4 • Absolute change from baseline in CFQ-R RD score at Week 4	• Absolute change from baseline in SwCl at Week 4 • Absolute change from baseline in CFQ-R RD score at Week 4
Other secondary endpoints	• Time-to-first PEx through Week 24 • Absolute change from baseline in BMI z-score at Week 24 • Absolute change from baseline in body weight at Week 24	

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; PD: pharmacodynamic(s); PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride

For the F/F population, endpoints that require a longer follow-up than 4 weeks were assessed in the open-label extension study 105 (i.e., pulmonary exacerbations [PEx], body mass index [BMI], and weight).

Spirometry was performed according to the internationally-recognized American Thoracic Society Guidelines/European Respiratory Society Guidelines.[1]

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) was used to capture and evaluate the impact of VX-445/TEZ/IVA on patient-reported respiratory symptoms and other aspects of health-related quality of life. In children of 12 and 13 years of age (at baseline) the CFQ-R for children was used, and a CFQ-R for Parents/Caregivers version.

PEx was defined as a clinical deterioration in respiratory status necessitating a change in antibiotic therapy (intravenous [IV], inhaled, or oral) for any 4 or more of the following signs or symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnoea; malaise, fatigue, or lethargy; temperature above 38°C (equivalent to approximately 100.4°F); anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of

[1] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

the chest; decrease in lung function by at least 10%; or radiographic changes indicative of pulmonary infection.

Sample size

Study 102 (F/MF)

Power calculations were based on 180 subjects and a 10% dropout rate in each treatment group at the final analysis and 70 subjects and a 5% dropout rate in each group at the IA.

Study 103 (F/F)

Power calculations were based on 100 subjects and a 5% dropout rate at Week 4.

Randomisation

For **Study 102** (F/MF), subjects with F/MF genotypes were randomized (1:1) to either VX 445/TEZ/IVA or placebo. Randomization was stratified by ppFEV1 determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 versus ≥18 years of age), and sex (male versus female).

For **Study 103** (F/F), subjects with the F/F genotype were randomized (1:1) to either VX 445/TEZ/IVA or TEZ/IVA. Randomization was stratified by ppFEV1 determined during the TEZ/IVA Run-in Period (<70 versus ≥70) and by age (<18 versus ≥18 years of age) at screening.

Blinding (masking)

For study 102 (F/MF) and study 103 (F/F), all subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were blinded to the treatment codes until the final database lock, with the following main exceptions:

• Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency or to ensure the safety of the subject and her foetus in the event of a pregnancy.

• For SAE processing and reporting regulations, for preparing the final (production) randomization list and for preparing the unblinded analysis for the IDMC.

• Bioanalytical contract research organization (CRO) analysing PK samples and the Vertex Bioanalytical personnel who is not a member of the study team but reviews raw data from the Bioanalytical CRO.

For study 102 only:

• Vendor for modelling and simulations performing population PK modelling in preparation for regulatory submission(s)

For the purpose of regulatory submissions in certain regions, a limited Vertex team may be unblinded to the IA results. The IA was performed by an external independent biostatistician who was not involved in and did not influence study conduct. The analyses generated by the external independent biostatistician were reviewed by the IDMC. Only after the IDMC declared that the study had crossed the prespecified efficacy boundary was the study unblinded by a limited Vertex team to prepare a regulatory submission. Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the study to protect the integrity of the study.

Statistical methods

Models

In both studies, analysis of the primary efficacy endpoint of absolute change from baseline in ppFEV1 was performed using a mixed-effects model for repeated measures (MMRM). A similar MMRM was used for all key secondary endpoints with the exception of the number of PEx (in Study 102) which used a negative binomial regression model. For the European Protocol all randomized subjects who carry the intended CFTR allele mutations and have received at least 1 dose of study drug.

Control of Overall Type I Error and Testing Hierarchy

Studies 102 and 103 each included a hierarchical testing procedure to control the type I error rate for the multiple key secondary endpoints which were tested at an alpha of 0.05. For a test at any step to be considered statistically significant within the testing hierarchy, it must have been statistically significant, and all previous tests (if any) within the hierarchy must have been statistically significant at the 0.05 level.

In the global protocol of Study 102, an interim analysis (IA) was planned for the testing of absolute change from baseline in $ppFEV_1$ at Week 4. For this, a Lan and DeMets alpha spending function was applied such that an alpha of 0.01 was preserved for the final analysis. Because all subjects were included in the IA, the information fraction was 100% and thus, the primary endpoint was tested at an alpha of 0.05 during the IA. This IA was not relevant to the European protocol because the primary endpoint for the European protocol regarded change through week 24.

Results

Participant flow

In study 102 (F/MF), of the 403 subjects who received at least 1 dose of study drug, 3 (0.7%) subjects (all in the VX-445/TEZ/IVA group) prematurely discontinued treatment (2 due to an AE, 1 due a pregnancy). A total of 13 (3.2%) had an important protocol deviation (IPD), related to prohibited medication, acute illness, safety assessment and study drug.

In study 103 (F/F), a total of 113 CF subjects were enrolled, of which 108 were randomized and 107 received at least 1 dose of study drug in the treatment period. No subjects discontinued study drug treatment during the Treatment Period. A total of 2 (1.9%) had an important protocol deviation (IPD) related to prohibited medication and safety assessment.

For both studies overall compliance was high.

Recruitment

Study 102 (F/MF) was conducted at 110 sites in US, Canada, Europe, and Australia.

Study 103 was conducted at 44 sites in US and Europe.

Conduct of the study

Study 102 was amended 2 times. Table 5 lists the global protocol versions and global amendment dates and summarizes the major changes in study conduct specified in each protocol amendment.

Table 5 Summary of Study 102 protocol amendments

Protocol Version	Date	Key changes
1.0	01 February 2018	Original version (no subjects enrolled under v1.0)
2.0	13 April 2018	• Updated the study drug regimen to include IVA in place of VX-561 (deuterated IVA), added the dose of study drug and tablet strength, and updated guidance on missed doses to account for q12h dosing of IVA. • Added a PK assessment 2 hours after the clinic dose. • Added specific guidance for study drug interruption for rash and clarified that that no dose modifications for toxicity were allowed. • Added vendor for modelling and simulations to the list of personnel who could be unblinded. • Updated statistical analysis plan section for clarity. • Edited categories of eligible mutations to better reflect the definition provided in the appendix
3.0	19 July 2018	• Removed G6PD deficiency and history of haemolysis as exclusion criteria; updated associated study drug interruption rules. • Updated text to reflect the current regulatory status of Symdeko/Symkevi.

CFQ-R RD: Cystic Fibrosis Questionnaire – Revised respiratory domain; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; PK: pharmacokinetic; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Baseline data

For study 102 and 103, the demographic and baseline characteristics are provided in Table 6 and Table 7, respectively. In general, the demographic and baseline characteristics are balanced between the two treatment groups.

Concomitant medications
The most common concomitant medications (continued and newly received) were medications typically used for management of CF.

For study 102, three antibiotic treatments were used more often in the placebo group: Tobramycin (55.7% in the Placebo group vs 39% in the active group), Ciprofloxacin (35% in the placebo group vs 16% of the active group) and Sulfamethoxazole and trimethoprim (26.1% of the placebo group vs 17.0% of the active group).

For study 103, omeprazole seems to be used slightly more often in the TEZ/IVA group (28.8%) compared to the active treatment group (18.2%).

Table 6: Studies 102 and 103: Subject Demographics, FAS

Characteristic	Study 102 (F/MF) Placebo N = 203	Study 102 (F/MF) VX-445/TEZ/IVA N = 200	Study 103 (F/F) TEZ/IVA N = 52	Study 103 (F/F) VX-445/TEZ/IVA N = 55
Age at baseline (years)				
Mean (SD)	26.8 (11.3)	25.6 (9.7)	27.9 (10.8)	28.8 (11.5)
Age groups at screening, n (%)				
≥12 to <18	60 (29.6)	56 (28.0)	14 (26.9)	16 (29.1)
≥18	143 (70.4)	144 (72.0)	38 (73.1)	39 (70.9)
Sex, n (%)				
Male	105 (51.7)	104 (52.0)	24 (46.2)	24 (43.6)
Female	98 (48.3)	96 (48.0)	28 (53.8)	31 (56.4)
Ethnicity, n (%)				
Hispanic or Latino	12 (5.9)	4 (2.0)	3 (5.8)	2 (3.6)
Not Hispanic or Latino	175 (86.2)	187 (93.5)	49 (94.2)	52 (94.5)
Not collected per local regulations	16 (7.9)	9 (4.5)	0	1 (1.8)
Race, n (%)				
White	184 (90.6)	186 (93.0)	52 (100.0)	54 (98.2)
Black or African American	2 (1.0)	4 (2.0)	0	0
Asian	1 (0.5)	0	0	0
American Indian or Alaska Native	1 (0.5)	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Not collected per local regulations	16 (7.9)	9 (4.5)	0	1 (1.8)
Other	1 (0.5)	2 (1.0)	0	0
Geographic Region, n (%)				
North America	120 (59.1)	118 (59.0)	33 (63.5)	34 (61.8)
Europe[a]	83 (40.9)	82 (41.0)	19 (36.5)	21 (38.2)

Sources: Study 102 CSR/Table 10-2 and Table 10-3; Study 103 CSR/Table 10-3 and Table 10-4
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
[a] In Study 102, the subgroup for Europe included subjects who were enrolled from Australia.

Table 7: Studies 102 and 103: Baseline Characteristics, FAS

Characteristic	Study 102 (F/MF) Placebo N = 203	Study 102 (F/MF) VX-445/TEZ/IVA N = 200	Study 103 (F/F) TEZ/IVA N = 52	Study 103 (F/F) VX-445/TEZ/IVA N = 55
Weight (kg)				
Mean (SD)	58.3 (12.7)	59.8 (12.9)	59.8 (14.8)	59.9 (12.7)
BMI (kg/m^2)				
Mean (SD)	21.31 (3.14)	21.49 (3.07)	21.88 (4.12)	21.75 (3.19)
ppFEV$_1$ (percentage points) at baseline				
Mean (SD)	61.3 (15.5)	61.6 (15.0)	60.2 (14.4)	61.6 (15.4)
ppFEV$_1$ category at baseline, n (%)				
<40	16 (7.9)	18 (9.0)	4 (7.7)	6 (10.9)
≥40 to <70	120 (59.1)	114 (57.0)	34 (65.4)	31 (56.4)
≥70 to ≤90	62 (30.5)	66 (33.0)	14 (26.9)	18 (32.7)
>90	5 (2.5)	2 (1.0)	0	0
SwCl (mmol/L) at baseline				
Mean (SD)	102.9 (9.8)[a]	102.3 (11.9)[a]	90.0 (12.3)[b]	91.4 (11.0)[b]
CFQ-R RD (points) at baseline				
Mean (SD)	70.0 (17.8)	68.3 (16.9)	72.6 (17.9)	70.6 (16.2)

Sources: Study 102 CSR/Table 10-3; Study 103 CSR/Table 10-4
BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor
[a] In Study 102, 201 subjects in the placebo group and 199 subjects in the VX-445/TEZ/IVA group had SwCl measurements at baseline.
[b] In Study 103, 52 subjects in the TEZ/IVA group and 54 subjects in the VX-445/TEZ/IVA group had SwCl measurements at baseline.

In terms of the F/MF genotypes represented in Study 102, the breakdown is provided in Table 8

Table 8: MF mutations (FAS) receiving placebo and the triple combination.

Table 10 Minimal Function (MF) Mutations by Treatment Group (Study 102 Full Analysis Set)

MF Mutation Subgroup	MF Mutation Category	MF Mutation	Placebo N = 203 n (%)	VX-445/TEZ/IVA N = 200 n (%)
Class I	Nonsense Mutations	G542X	40 (19.7)	25 (12.5)
		W1282X	9 (4.4)	9 (4.5)
		R553X	11 (5.4)	8 (4.0)
		R1162X	7 (3.4)	7 (3.5)
		R1158X	0	3 (1.5)
		S489X	1 (0.5)	3 (1.5)
		Y1092X	3 (1.5)	3 (1.5)
		Q39X	0	2 (1.0)
		Q493X	3 (1.5)	2 (1.0)
		R709X	0	2 (1.0)
		W846X	1 (0.5)	2 (1.0)
		E585X	0	1 (0.5)
		E60X	5 (2.5)	1 (0.5)
		E92X	0	1 (0.5)
		G330X	0	1 (0.5)
		R851X	0	1 (0.5)
		W1204X	0	1 (0.5)
		W401X	0	1 (0.5)
		W496X	0	1 (0.5)
		E1371X	1 (0.5)	0
		K710X	2 (1.0)	0
		L88X	1 (0.5)	0
		Q1313X	1 (0.5)	0
		Q220X	1 (0.5)	0
		R1102X	1 (0.5)	0
		S466X	1 (0.5)	0
		W1089X	1 (0.5)	0
Class I	Splice Mutations	621+1G>T	13 (6.4)	14 (7.0)
		1717-1G>A	12 (5.9)	12 (6.0)
		1898+1G>A	4 (2.0)	4 (2.0)
		3120+1G>A	0	2 (1.0)
		1249-1G>A	0	1 (0.5)
		2622+1G>A	3 (1.5)	1 (0.5)
		406-1G>A	0	1 (0.5)
		406-2A>G	0	1 (0.5)
		3040G>C (G970R)	0	1 (0.5)
		1248+1G>A	1 (0.5)	0
		1525-2A>G	1 (0.5)	0
		1717-8G>A	1 (0.5)	0
		1812-1G>A	1 (0.5)	0

MF Mutation Subgroup	MF Mutation Category	MF Mutation	Placebo N = 203 n (%)	VX-445/TEZ/IVA N = 200 n (%)
		296+1G>A	1 (0.5)	0
		3121-1G>A	1 (0.5)	0
		711+1G>T	1 (0.5)	0
		712-1G>T	1 (0.5)	0
Class I	Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	3659delC	3 (1.5)	7 (3.5)
		2183AA>G	0	5 (2.5)
		1154insTC	3 (1.5)	4 (2.0)
		3905insT	1 (0.5)	4 (2.0)
		394delTT	1 (0.5)	3 (1.5)
		2143delT	0	2 (1.0)
		1548delG	0	1 (0.5)
		2184delA	0	1 (0.5)
		2184insA	7 (3.4)	1 (0.5)
		3007delG	1 (0.5)	1 (0.5)
		3878delG	0	1 (0.5)
		4016insT	1 (0.5)	1 (0.5)
		908delT	0	1 (0.5)
		1078delT	4 (2.0)	0
		182delT	1 (0.5)	0
		3876delA	2 (1.0)	0
		457TAT>G	1 (0.5)	0
		663delT	1 (0.5)	0
Class I	Non-small (>3 nucleotide) ins/del frameshift mutations	CFTR dele2, 3	4 (2.0)	7 (3.5)
		4209TGTT>AA	0	1 (0.5)
		CFTRdele17a,17b	0	1 (0.5)
		CFTRdele22-24	1 (0.5)	1 (0.5)
		852del22	1 (0.5)	0
Non-Class I	Missense or in-frame deletions	N1303K	21 (10.3)	19 (9.5)
		R347P	3 (1.5)	7 (3.5)
		G85E	3 (1.5)	5 (2.5)
		I507del	5 (2.5)	4 (2.0)
		R1066C	2 (1.0)	3 (1.5)
		R560T	3 (1.5)	3 (1.5)
		V520F	1 (0.5)	2 (1.0)
		A559T	1 (0.5)	1 (0.5)
		L1077P	0	1 (0.5)
		L467P	2 (1.0)	1 (0.5)
		M1101K	0	1 (0.5)
		3199del6	1 (0.5)	0

Source: Study 102 Ad hoc Table 14.1.10

IVA: ivacaftor; TEZ: tezacaftor

Note: Only the MF allele is shown; all subjects were heterozygous for *F508del* and the listed MF mutation. Table is sorted in descending order of frequency of the VX-445/TEZ/IVA column by MF mutation for each MF mutation category.

Numbers analysed

The efficacy analyses of study 102 (n=403) and 103 (n=107) were performed on the Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutations and have received at least 1 dose of study drug.

The modified FAS (m-FAS) excluded patients that did not meet the eligibility criteria or with significant deviations of study drug administration. In study 102, 2 patients were excluded (from placebo arm only) for the m-FAS and 8 patients (5 placebo, 3 active arm) were excluded from the mFAS analysis of

SwCl (pre-dose SwCl value <60.0 mmol/L). In 103, no m-FAS analysis was performed, as all patients met the criteria.

From study 102, all 400 patients that complete dosing rolled over to the open-label study (Study 105).

From study 103, all 107 patients rolled over to the open-label study (Study 105).

Outcomes and estimation

- *Primary endpoint – Absolute change in ppFEV1*

In Study **102**, treatment with VX-445/TEZ/IVA resulted in a statistically significant improvement in absolute change in ppFEV1 through Week 24 compared to placebo, with a treatment difference of 14.3 percentage points (P<0.0001). Improvements in ppFEV1 were already seen at week 4 (secondary endpoints), with a statistically significant treatment difference of 13.7 percentage points (P<0.0001) (Table 9 and Figure 3).

In Study **103**, following a 4-week TEZ/IVA run-in, treatment with VX-445/TEZ/IVA resulted in a statistically significant and clinically meaningful improvement in absolute change in ppFEV1 at Week 4 compared to TEZ/IVA, with a treatment difference of 10.0 percentage points (P<0.0001) (

Table 10 and Figure 4).

Table 9: Study 102 (F/MF): Absolute change from baseline in ppFEV1 through week 24 (percentage points)

Analysis	Statistic	Placebo N = 203	VX-445/TEZ/IVA N = 200
Primary Endpoint			
European Protocol: Absolute change from baseline in ppFEV$_1$ through Week 24 (percentage points)	n	203	196
	LS mean (SE)	-0.4 (0.5)	13.9 (0.6)
	95% CI of LS mean	(-1.5, 0.7)	(12.8, 15.0)
	LS mean difference, 95% CI	--	**14.3 (12.7, 15.8)**
	P value versus placebo	--	<0.0001

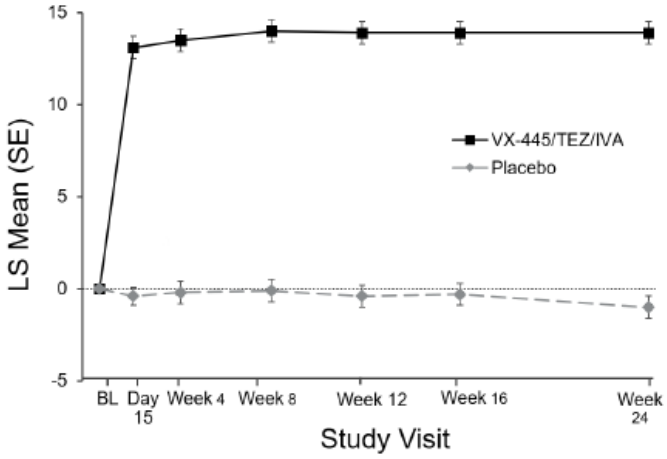
Source: Module 2.7.3/Table 9
FAS: Full Analysis Set; iFAS: Interim Full Analysis Set; IVA: ivacaftor; LS: least squares; ppFEV1: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Table 10: Study 103 (F/F): Absolute change from baseline in ppFEV1 at week 4 (percentage points)

Endpoint (Analysis Set)	Statistic	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Absolute change from baseline in ppFEV$_1$ at Week 4 (FAS)	n	49	53
	LS mean (SE)	0.4 (0.9)	10.4 (0.9)
	95% CI of LS mean	(-1.4, 2.3)	(8.6, 12.2)
	LS mean diff, 95% CI	--	**10.0 (7.4, 12.6)**
	P value vs. TEZ/IVA	--	<0.0001

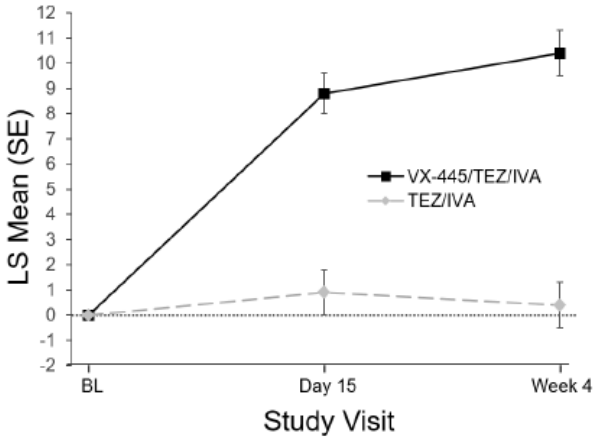
Source: Module 2.7.3/Table 12
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Figure 3: Study 102 (F/MF): Absolute change from baseline in ppFEV1 by Visit (percentage points)



Source: Module 2.7.3/Figure 3
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the final analysis.

Figure 4: Study 103 (F/F): absolute change from baseline in ppFEV1 by Visit (percentage points)



Source: Module 2.7.3/Figure 10
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the final analysis.

- *Key secondary endpoint – SwCl*

In Study **102**, treatment with VX-445/TEZ/IVA resulted in a statistically significant improvement in absolute change in SwCl through Week 24 with a treatment difference of -41.8 mmol/L (P<0.0001) compared to placebo (Table 11 and Figure 5).

In Study **103**, following a 4-week TEZ/IVA run-in, statistically, significant improvements were also observed at Week 4 with a treatment difference of -45.1 mmol/L for VX-445/TEZ/IVA versus TEZ/IVA (P<0.0001) (Table 12 and Figure 6).

Table 11: Study 102 (F/MF): Absolute change from baseline in SwCl through week 24 (mmol/L)

Endpoint (Analysis Set)	Statistic	Placebo N = 203	VX-445/TEZ/IVA N = 200
Absolute change from baseline in SwCl through Week 24 (FAS)	n	201	199
	LS mean (SE)	-0.4 (0.9)	-42.2 (0.9)
	95% CI of LS mean	(-2.2, 1.4)	(-44.0, -40.4)
	LS mean diff, 95% CI	--	**-41.8 (-44.4, -39.3)**
	P value vs. placebo	--	<0.0001

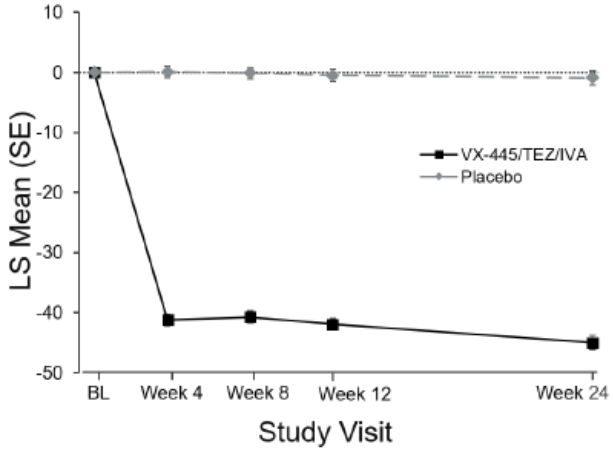
Source: Module 2.7.3/Table 9
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; SwCl: sweat chloride; TEZ: tezacaftor

Table 12: Study 103 (F/F): Absolute change from baseline in SwCl at week 4 (mmol/L)

Endpoint (Analysis Set)	Statistic	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Absolute change from baseline in SwCl at Week 4 (FAS)	n	48	54
	LS Mean (SE)	1.7 (1.8)	-43.4 (1.7)
	95% CI of LS Mean	(-1.9, 5.3)	(-46.9, -40.0)
	LS Mean Diff, 95% CI	--	**-45.1 (-50.1, -40.1)**
	P value vs. TEZ/IVA	--	<0.0001

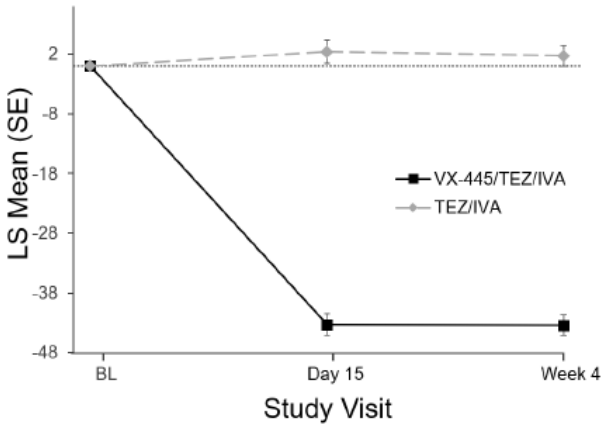
Source: Module 2.7.3/Table 12
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; SwCl: sweat chloride; TEZ: tezacaftor

Figure 5: Study 102 (F/MF): Absolute change from baseline in SwCl by Visit (mmol/L)



Source: Module 2.7.3/Figure 5
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor
Notes: The y-axis corresponds to the LS means from the models at the final analysis.

Figure 6: Study 103 (F/F): Absolute change from baseline in SwCl by Visit (mmol/L)



Source: Module 2.7.3/Figure 11
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor
Notes: The y-axis corresponds to the LS means from the MMRM models at the final analysis.

- *Key secondary endpoint – Respiratory Symptoms*

In Study **102**, treatment with VX-445/TEZ/IVA resulted in a statistically significant improvement in absolute change in CFQ-R RD score through Week 24 with a treatment difference of 20.2 points (P<0.0001) compared to placebo (Table 13).

In Study **103**, statistically significant improvements were also observed at Week 4 with a treatment difference of 17.4 points for VX-445/TEZ/IVA versus TEZ/IVA (P<0.0001) (Table 14).

Table 13 Study 102 (F/MF): Absolute change from baseline in CFQ-R RD Score through 24 weeks (points)

Endpoint (Analysis Set)	Statistic	Placebo N = 203	VX-445/TEZ/IVA N = 200
Absolute change from baseline in CFQ-R RD score through Week 24 (FAS)	n	203	200
	LS mean (SE)	-2.7 (1.0)	17.5 (1.0)
	95% CI of LS mean	(-4.6, -0.8)	(15.6, 19.5)
	LS mean diff, 95% CI	--	**20.2 (17.5, 23.0)**
	P value vs. placebo	--	<0.0001

Source: Module 2.7.3/Table 9
CFQ-R: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; RD: respiratory domain; TEZ: tezacaftor

Table 14 Study 103 (F/F): Absolute change from baseline in CFQ-R RD Score at week 4 (points)

Endpoint (Analysis Set)	Statistic	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Absolute change from baseline in CFQ-R RD score at Week 4 (FAS)	n	52	55
	LS mean (SE)	-1.4 (2.0)	16.0 (2.0)
	95% CI of LS mean	(-5.4, 2.6)	(12.1, 19.9)
	LS mean diff, 95% CI	--	**17.4 (11.8, 23.0)**
	P value vs. TEZ/IVA	--	<0.0001

Source: Module 2.7.3/Table 12
CRQ-R: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; RD: respiratory domain; TEZ: tezacaftor

- *Key secondary endpoint – Pulmonary Exacerbations (only study 102)*

In Study **102**, VX-445/TEZ/IVA resulted in a statistically significant reduction in PEx through Week 24, with a PEx rate that was 63% lower in the VX-445/TEZ/IVA group than the placebo group (rate ratio = 0.37 [*P*<0.0001; 95% CI: 0.25, 0.55]). The annual event rate was 0.37 in the VX-445/TEZ/IVA group versus 0.98 in the placebo group.

Analysis of time-to-first PEx through Week 24 showed that a greater proportion of subjects in the VX-445/TEZ/IVA group remained free of PEx than the proportion of subjects in the placebo group. The risk of a PEx is reduced when treated with the triple combination (HR: 0.34; 95% CI 0.22, 0.52; p<0.0001).

Table 15 Negative binomial analysis of the number of pEx during the PEx analysis period (FAS)

	Placebo N = 203	VX-445/TEZ/IVA N = 200
Number of subjects with events, n (%)	76 (37.4)	31 (15.5)
Number of events	113	41
Estimated event rate per year	0.98	0.37
Rate ratio, 95% CI	--	0.37 (0.25, 0.55)
P value versus placebo	--	<0.0001

For subjects included in study 103, results on nutritional status will be displayed with study 105.

- *Key secondary endpoint – Nutritional status (only study 102)*

In Study **102**, statistically significant improvements were observed for absolute change from baseline in BMI, with a treatment difference of 1.04 kg/m2 (*P*<0.0001) for VX-445/TEZ/IVA versus placebo at Week 24. Improvements were also observed for absolute change from baseline in BMI z-score and body weight at Week 24, with a treatment difference in BMI z-score of 0.30 (nominal *P*<0.0001) and a treatment difference in body weight of 2.9 kg (nominal *P*<0.0001) for VX-445/TEZ/IVA versus placebo (Table 16).

For subject included in study 103, results on nutritional status will be displayed at study 105.

Table 16 Study 102 (F/MF): Absolute change from baseline in BMI at week 24 (kg/m^2)

Endpoint (Analysis Set)	Statistic	Placebo N = 203	VX-445/TEZ/IVA N = 200
Absolute change from baseline in BMI at Week 24 (FAS)	n	202	198
	LS mean (SE)	0.09 (0.07)	1.13 (0.07)
	95% CI of LS mean	(-0.05, 0.22)	(0.99, 1.26)
	LS mean diff, 95% CI	--	**1.04 (0.85, 1.23)**
	P value vs. placebo	--	<0.0001

Source: Module 2.7.3/Table 9
BMI: body mass index; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; TEZ: tezacaftor

Ancillary analyses

Efficacy subsets (m-FAS)

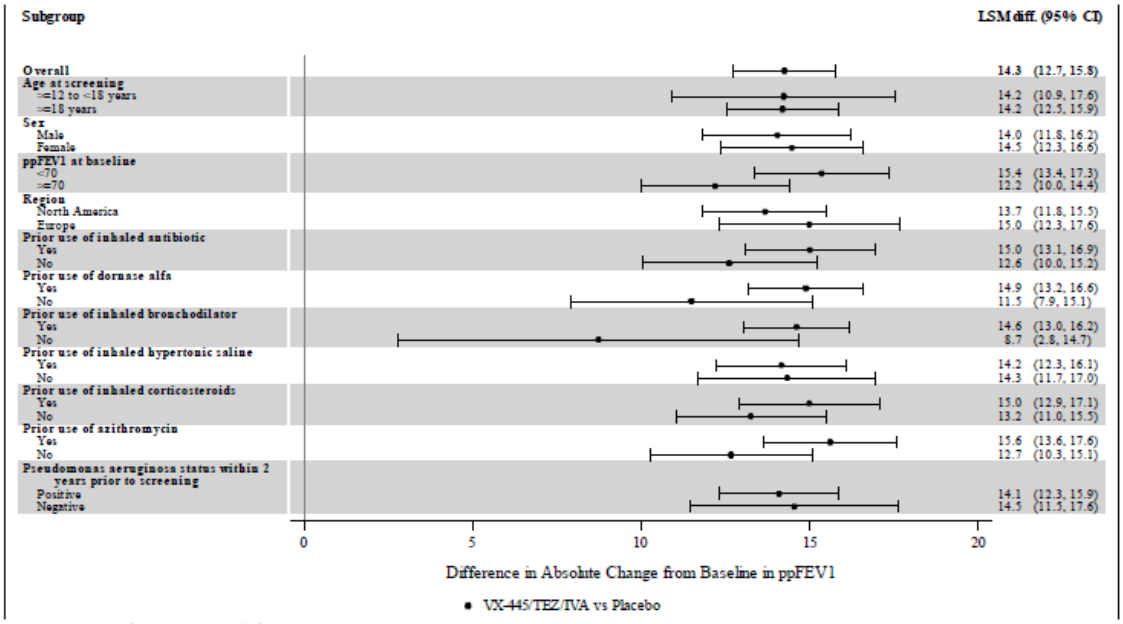
For study 102, results from the M-FAS were consistent with the analysis performed by the FAS.

For study 103, no analyses were done using subset of subjects in the FAS.

Subgroup analyses

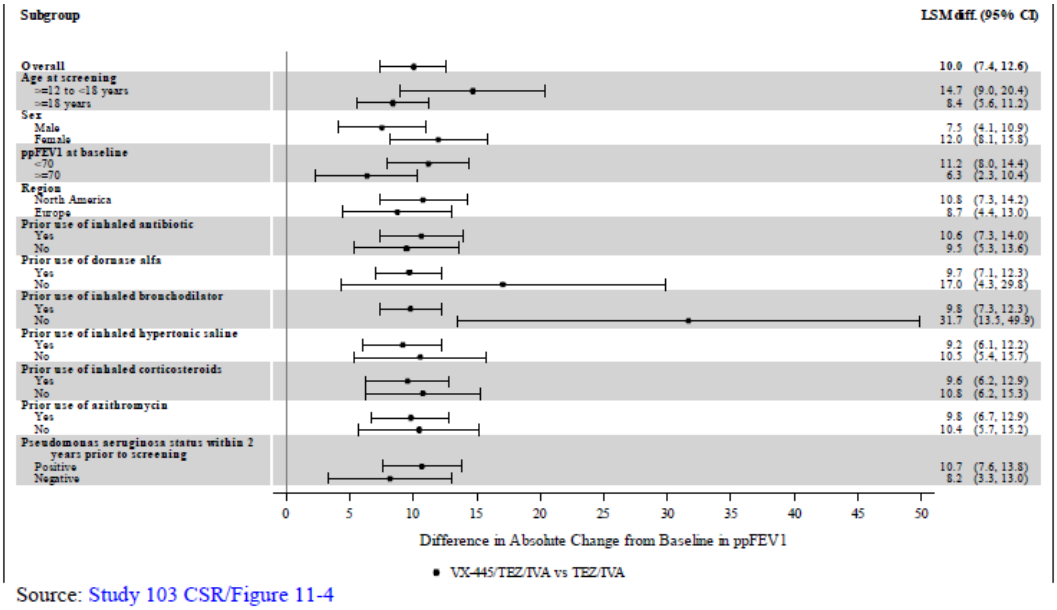
Prespecified subgroup analyses of the absolute change in ppFEV1 from baseline were performed similarly to the primary analysis. For both studies, the results of the subgroup analyses were consistent with the results of the primary analyses. Due to the small size of study 103, some subgroups have a limited number of subjects (Figure 7 and Figure 8).

Figure 7: Study 102 (F/MF Subjects): Subgroup analysis for absolute change from baseline in ppFEV1 Through week 24 (percentage points), FAS



Source: Study 102 CSR/Figure 11-8

Figure 8: Study 103 (F/F Subjects): Subgroup analysis for absolute change from baseline in ppFEV1 at week 4 (percentage points), FAS



Source: Study 103 CSR/Figure 11-4

To further explore the hypothesis that a single *F508del* allele is sufficient to provide substantial clinical efficacy, an ad hoc analysis was performed to assess outcomes in F/MF subjects in Study 102 with a

Class I MF mutation (n = 314, ~78% of the overall study population) (criterion 1) and patients not responding in vitro to IVA or TEZ/IVA (missense or in-frame deletion, criterion 2). Treatment of these subjects with VX-445/TEZ/IVA resulted in an absolute change from baseline in ppFEV1 through Week 24 of 14.8 percentage points when compared to placebo for patient included based on criterion 1 and of 12.9 percentage points for patients included based on criterion 2). The outcome of this analysis was similar to the overall study outcome (14.3 percentage points) (See Table 17).

Table 17 MMRM Analysis of Absolute Change from Baseline in ppFEV1 through Week 24 by Genotype (FAS)

	Placebo N = 203	VX-445/TEZ/IVA N = 200
Genotype Subgroup: Missense and in-frame deletions		
n	42	47
LS mean (SE)	-0.7 (1.0)	12.2 (0.9)
95% CI of LS mean	(-2.8, 1.3)	(10.3, 14.0)
LS mean difference, 95% CI	--	12.9 (10.1, 15.7)
Genotype Subgroup: Class I		
n	161	149
LS mean (SE)	-0.3 (0.6)	14.4 (0.7)
95% CI of LS mean	(-1.6, 0.9)	(13.1, 15.8)
LS mean difference, 95% CI	--	14.8 (13.0, 16.6)

Source: Ad hoc Table 14.2.8.11

In addition, these subgroups were further subdivided. The outcome of these post-hoc analyses was similar to the overall study outcome (Table 18, Table 19, Table 20).

Table 18 Absolute Change from Baseline in ppFEV1 (mean difference) through Week 24 by Criterion 1 subgroups

	ppFEV1	**SwCl**
Criterion 1 mutation	**14.8 (13.0, 16.6)**	**-42.1 (-44.8, -39.3)**
Nonsense	14.0 (11.5, 16.6)	-38.8 (-42.5, -35.0)
Splice	17.8 (13.7, 21.8)	-45.3 (-50.3, -40.3)
Indel-frameshift	12.9 (9.3, 16.5)	-41.6 (-47.8, -35.4)

Table 19 Absolute Change from Baseline in ppFEV1 through Week 24 by Genotype subgroups

	ppFEV1	**SwCl**
Criterion 2 mutation	**12.2 (10.3, 14.0)**	
Responsive in FRT	13.5 (9.6, 16.3)	-52.3 (-61.3, -41.3)
Non-responsive in FRT	11.0 (8.8, 13.6)	-41.8 (-46.2, -30.9)

Table 20 Absolute Change from Baseline in ppFEV1 and SwCl through Week 24 in subgroups that will (likely) not form a CFTR protein

	Sample Size	**LS Mean Difference (95% CI)**	
	N	**$ppFEV_1$ (percentage points)**	**SwCl (mmol/L)**
Study 102 (all subjects)	403	14.3 (12.7, 15.8)	-41.8 (-44.4, -39.3)
MF Class I mutations	314	14.8 (13.0, 16.6)	-42.1 (-44.8, -39.3)
Stop codon prior to NBD2 domain	142	13.2 (10.4, 16.0)	-36.6 (-40.5, -32.7)
***G542X* only**	65	13.6 (9.4, 17.7)	-38.7 (-44.0, -33.4)

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21 Summary of efficacy for Study VX17-445-102

Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF).			
Study identifier	EudraCT Number: 2018-000183-28		
Design	Randomized, double-blind, placebo-controlled, parallel-group, mulicenter, 12 years and older, CF, heterozygous F/MF		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks Not applicable As extension part, patients rolled in a separate study
Hypothesis	Superiority		
Treatments groups	VX-445 + tezacaftor + ivacaftor		200mg VX-445/100 mg TEZ/150 mg IVA daily for 24 weeks + 150 mg IVA daily for 24 weeks. N=201 (randomized)
	Placebo		0 mg VX-445/0 mg TEZ/0 mg IVA daily for 24 weeks + 0 mg IVA daily for 24 weeks. N=204 (randomized)
Endpoints and definitions	Primary endpoint	ppFEV1	Absolute change in ppFEV1 from baseline through Week 24
	Key Secondary	ppFEV1	Absolute change in ppFEV1 from baseline at Week 4
	Key Secondary	PEx	Number of Pulmonary Exacerbations Through Week 24
	Key Secondary	SwCl	Absolute Change in SwCl From Baseline Through Week 24
	Key Secondary	CFQ-R	Absolute Change in CFQ-R RD Score From Baseline Through Week 24
	Key Secondary	BMI	Absolute Change in BMI From Baseline at Week 24
Database lock	24 April 2019 (date last subject completed the last visit)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutations and received at least 1 dose of study drug – 24 weeks		
Descriptive statistics and estimate variability	Treatment group	placebo	VX-445/TEZ/IVA
	Number of subjects	203	200
	LS mean ppFEV1 (week 24)	-0.4	13.9

	95% CI of LS mean	(-1.5, 0.7)	(12.8, 15.0)
	LS mean ppFEV1 (week 4)	-0.2	13.5
	95% CI of LS mean	(-1.3, 1.0)	(12.3, 14.7)
	PEx (number)	113	41
	Estimated event rate per year	0.98	0.37
	LS mean SwCl	-0.4	-42.2
	95% CI of LS mean	(-2.2, 1.4)	(-44.0, -40.4)
	LS mean CFQ-R RD	-2.7	17.5
	95% CI of LS mean	(-4.6, -0.8)	(15.6, 19.5)
	LS mean BMI	0.09	1.13
	95% CI of LS mean	(-0.05, 0.22)	(0.99, 1.26)

Effect estimate	Primary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference ppFEV1 – week 24	14.3
		95% CI	12.7, 15.8
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference ppFEV1 – week 4	13.7
		95% CI	12.0, 15.3
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		Rate reduction in PExs	0.37
		95% CI	0.25, 0.55
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference SwCl	-41.8
		95% CI	-44.4, -39.3
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference CFQ-R RD	20.2
		95% CI	17.5, 23.0
		P-value	<0.0001
	Key secondary	Comparison groups	VX-445/TEZ/IVA vs placebo

	endpoint	LS mean difference BMI	1.04
		95% CI	0.85, 1.23
		P-value	<0.0001
Notes	All primary and key secondary endpoints were controlled for multiplicity and were statistically significant in the framework of the testing hierarchy.		
Analysis description	**Secondary analysis** As other secondary efficacy endpoints, Absolute Change in SwCl From Baseline at Week 4, Absolute Change in CFQ-R RD Score From Baseline at Week 4, Time-to-first PEx Through Week 24, Absolute Change in BMI Z-score From Baseline at Week 24 and Absolute Change in Body Weight From Baseline at Week 24 were investigated. They all showed a positive effect for VX-445/TEZ/IVA compared to placebo. **Ancillary analysis** The Forest Plot for the subgroups analysed, shows a consistent beneficial effect for VX-445/TEZ/IVA compared to placebo.		

Table 22 Summary of efficacy for Study VX17-445-103

Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for the *F508del* Mutation (F/F)			
Study identifier	EudraCT Number: 2018-000184-89		
Design	Randomized, double-blind, active-controlled, parallel-group, multicenter, 12 years and older, CF, homozygous F/F		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		4 weeks 4 weeks (on TEZ/IVA) As extension part, patients rolled in a separate study
Hypothesis	Superiority		
Treatments groups	VX-445 + tezacaftor + ivacaftor		200mg VX-445/100 mg TEZ/150 mg IVA daily for 4 weeks + 150 mg IVA daily for 4 weeks. N=56 (randomized)
	Tezacaftor + ivacator		100 mg TEZ/150 mg IVA daily for 4 weeks + 150 mg IVA daily for 24 weeks. N=52 (randomized)
Endpoints and definitions	Primary endpoint	ppFEV1	Absolute change in ppFEV1 from baseline at week 4
	Key Secondary	SwCl	Absolute Change in SwCl From Baseline at week 4
	Key Secondary	CFQ-R	Absolute Change in CFQ-R RD Score From Baseline Through at week 4
Database lock	28 December 2018 (date last subject completed the last visit)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutations and received at least 1 dose of study drug – 4 weeks		

Descriptive statistics and estimate variability	Treatment group	TEZ/IVA	VX-445/TEZ/IVA
	Number of subjects	52	55
	LS mean ppFEV1 (week 4)	0.4	10.4
	95% CI of LS mean	(-1.4, 2.3)	(8.6, 12.2)
	LS mean SwCl	1.7	-43.4
	95% CI of LS mean	(-1.9, 5.3)	(-46.9, -40.0)
	LS mean CFQ-R RD	-1.4	16.0
	95% CI of LS mean	(-5.4, -2.6)	(12.1, 19.9)

Effect estimate	Primary endpoint	Comparison groups	VX-445/TEZ/IVA vs TEZ/IVA
		LS mean difference ppFEV1 – week 4	10.0
		95% CI	7.4, 12.6
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs TEZ/IVA
		LS mean difference SwCl	-45.1
		95% CI	-50.1, -40.1
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs TEZ/IVA
		LS mean difference CFQ-R RD	17.4
		95% CI	11.8, 23.0
		P-value	<0.0001
Notes	All primary and key secondary endpoints were controlled for multiplicity and were statistically significant in the framework of the testing hierarchy.		
Analysis description	**Ancillary analysis** The Forest Plot for the subgroups analysed, shows a consistent beneficial effect for VX-445/TEZ/IVA compared to placebo.		

Clinical studies in special populations

All trials included adolescents and adults.

Subgroup analyses of the primary endpoint were performed using a model similar to that for the primary analysis. Subgroup analyses showed consistent changes in ppFEV1 regardless of age, sex, baseline lung function, geographic region, prior use of common CF medications, and *P. aeruginosa* colonization.

Studies 102 and 103 excluded pregnant and lactating women, and also excluded subjects with a history of any illness or condition that could confound study results or pose an additional safety risk (e.g., clinically significant hepatic cirrhosis with or without portal hypertension).

Both studies did not include any patients aged 65 years and older; thus, it is not known whether they respond differently from younger adults patients.

Supportive study

Study VX17-445-105
Open-label extension study in subjects that completed study treatment in study 102 and 103.

Subjects who completed Studies 102 (n=400) and 103 (n=107) and met eligibility criteria were enrolled in OLE Study 105. All subjects receive the same dose of VX 445/TEZ/IVA as the VX 445/TEZ/IVA arms of Studies 102 and 103. The treatment duration in Study 105 is 96 weeks. This duration is considered sufficient for the evaluation of long-term safety and efficacy.

The primary objective of Study 105 is safety. The secondary efficacy endpoints in Study 105 are similar to the pivotal studies 102 and 103 (e.g. ppFEV1, PEx, SwCL, CFQ-R RD, BMI).

Updated Interim Analysis study data (IA2) are provided for F/MF (study 102) and F/F subjects (study 103) with data cut-off date of 31 October 2019.

Results for F/MF subjects

Two subjects in each group (original arm from study 102) discontinued treatment due to an AE.

Efficacy results are provided in Table 23, Figure 9 and Figure 10.

Table 23 Study 105 IA2 (F/MF Subjects): Secondary Efficacy Analyses, OL-FAS

		OL Week 24	
Analysis	Statistic	Placebo in Study 102 N = 203	VX-445/TEZ/IVA in Study 102 N = 196
Absolute change from baseline in ppFEV$_1$ (percentage points)	n	189	180
	LS mean (SE)	14.9 (0.7)	14.3 (0.7)
	95% CI of LS mean	(13.5, 16.3)	(12.9, 15.7)
Number of PEx[a]	n	203	200
	Number of subjects with events, n (%)	35 (17.2)	55 (27.5)
	Number of events	44	84
	Estimated event rate per year (95% CI)	0.27 (0.19, 0.39)	0.32 (0.24, 0.44)
Absolute change from baseline in SwCl (mmol/L)	n	187	183
	LS mean (SE)	-50.3 (1.3)	-49.0 (1.3)
	95% CI of LS mean	(-52.9, -47.8)	(-51.6, -46.4)
Absolute change from baseline in CFQ-R RD score (points)	n	197	192
	LS mean (SE)	19.2 (1.3)	20.1 (1.3)
	95% CI of LS mean	(16.7, 21.7)	(17.6, 22.6)
Absolute change from baseline in BMI (kg/m^2)	n	196	190
	LS mean (SE)	1.21 (0.09)	1.28 (0.10)
	95% CI of LS mean	(1.03, 1.40)	(1.09, 1.46)
Absolute change from baseline in BMI z-score[b]	n	63	62
	LS mean (SE)	0.43 (0.07)	0.33 (0.07)
	95% CI of LS mean	(0.29, 0.57)	(0.19, 0.48)
Absolute change from baseline in body weight (kg)	n	196	190
	LS mean (SE)	3.9 (0.3)	4.1 (0.3)
	95% CI of LS mean	(3.4, 4.4)	(3.5, 4.6)

Sources: IA2 Tables 14.2.2.1.1, 14.2.3.2.1, 14.2.4.2.1, 14.2.5.2.1, 14.2.6.2.1, 14.2.6.4.1, and 14.2.6.6.1

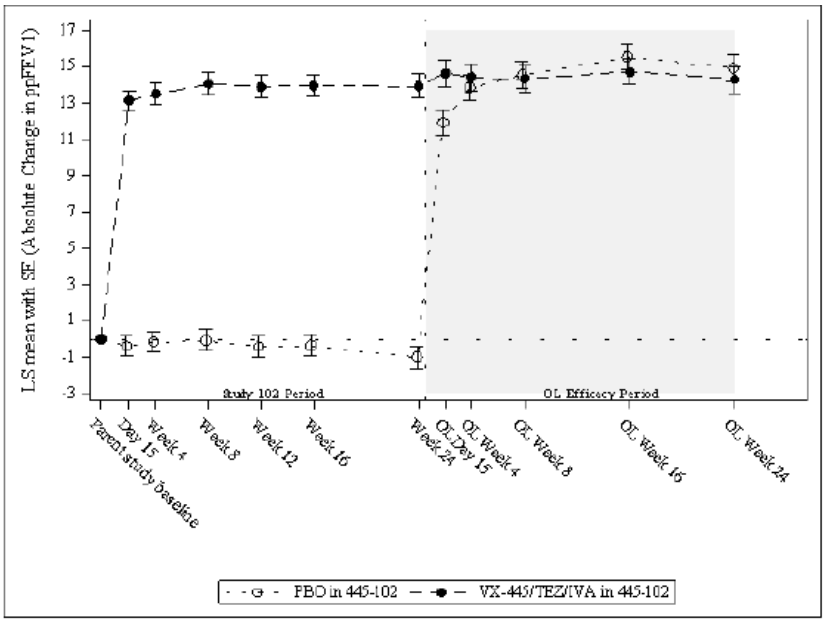
BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; OL: open label; PEx: pulmonary exacerbation; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor

[a] PEx was analyzed including data from the parent study.

[b] BMI z-score was analyzed for subjects ≤20 years old on the date of informed consent in the parent study.

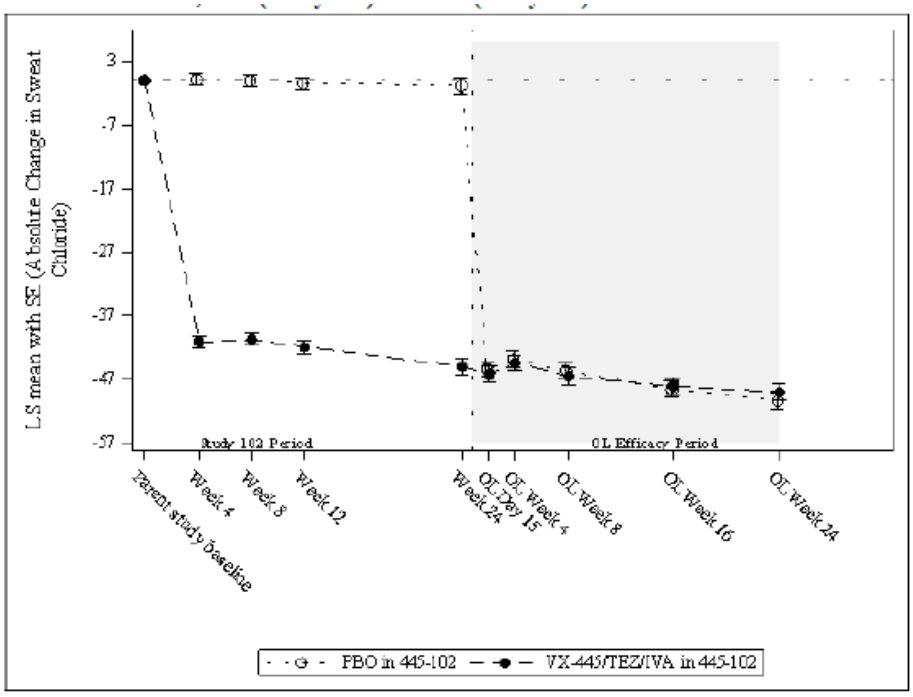
Note: Baseline is the parent study baseline, which was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study.

Figure 9: Study 105 IA2 (F/MF Subjects): Absolute Change From Baseline in $ppFEV_1$ (Percentage Points) by Visit, FAS (Study 102)/OL-FAS (Study 105)



Source: IA2 Figure 14.2.1.1
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open label; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

Figure 10: Study 105 IA2 (F/MF Subjects): Absolute Change From Baseline in SwCl (mmol/L) by Visit, FAS (Study 102)/OL-FAS (Study 105)



Source: IA2 Figure 14.2.2.1
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open label; PBO: placebo; SwCl: sweat chloride; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

Results for F/F subjects

In the VX-445/TEZ/IVA arm 1 subject and in the TEZ/IVA arm 2 subjects (original arm from study 103) discontinued treatment due to an AE.

Efficacy results are provided in Table 24,

Figure 11 and Figure 12.

Table 24 Study 105 IA2 (F/F Subjects): Secondary Efficacy Analyses, OL-FAS

		OL Week 36	
Analysis	Statistic	TEZ/IVA in Study 103 N = 52	VX-445/TEZ/IVA in Study 103 N = 55
Absolute change from baseline in ppFEV$_1$ (percentage points)	n	49	51
	LS mean (SE)	12.8 (1.3)	11.9 (1.3)
	95% CI of LS mean	(10.1, 15.4)	(9.3, 14.5)
Number of PEx[a]	N	107	
	Number of subjects with events, n (%)	27 (25.2)	
	Number of events	33	
	Estimated event rate per year (95% CI)	0.30 (0.20, 0.45)	
Absolute change from baseline in SwCl* (mmol/L)	n	48	50
	LS mean (SE)	-49.4 (2.5)	-47.2 (2.4)
	95% CI of LS mean	(-54.3, -44.5)	(-52.0, -42.5)
Absolute change from baseline in CFQ-R RD score* (points)	n	51	54
	LS mean (SE)	13.8 (2.5)	14.3 (2.4)
	95% CI of LS mean	(8.9, 18.8)	(9.5, 19.2)
Absolute change from baseline in BMI (kg/m^2)	n	51	53
	LS mean (SE)	1.18 (0.18)	1.30 (0.18)
	95% CI of LS mean	(0.82, 1.54)	(0.95, 1.65)
Absolute change from baseline in BMI z-score[b]	n	16	15
	LS mean (SE)	0.32 (0.10)	0.30 (0.10)
	95% CI of LS mean	(0.11, 0.53)	(0.09, 0.52)
Absolute change from baseline in body weight (kg)	n	51	53
	LS mean (SE)	3.6 (0.5)	4.0 (0.5)
	95% CI of LS mean	(2.6, 4.6)	(3.0, 5.0)

Sources: IA2 Tables 14.2.2.1.2, 14.2.3.2.2, 14.2.4.2.2, 14.2.5.2.2, 14.2.6.2.2, 14.2.6.4.2, and 14.2.6.6.2

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; OL: open label; PEx: pulmonary exacerbation; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

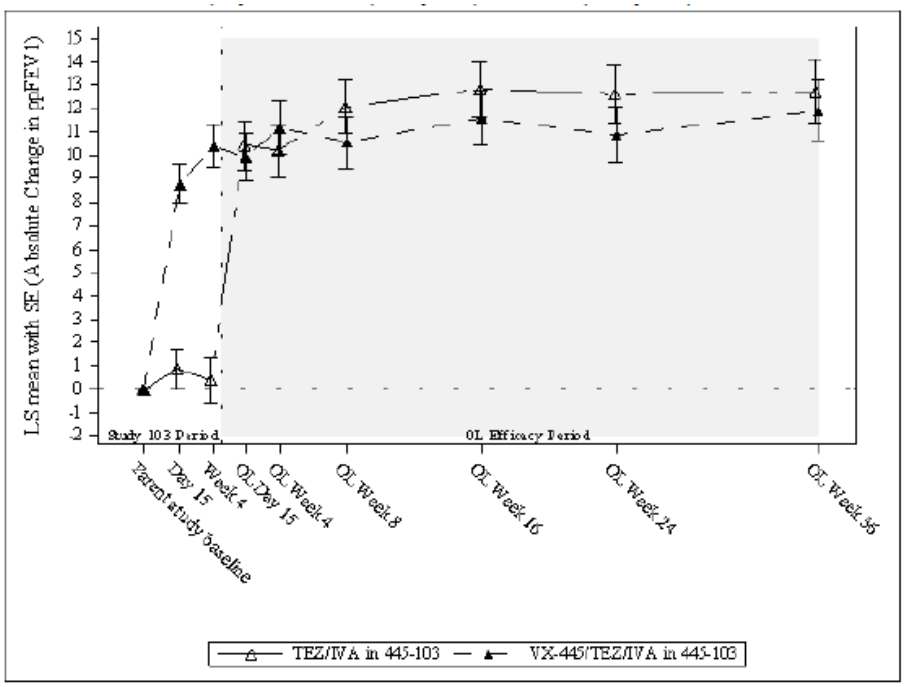
* SwCl and CFQ-R RD were not collected at OL Week 36; the results shown include data through OL Week 24.

[a] PEx was analyzed including data from the parent study and the treatment groups from Study 103 were pooled for the analysis.

[b] BMI z-score was analyzed for subjects ≤20 years old on the date of informed consent in the parent study.

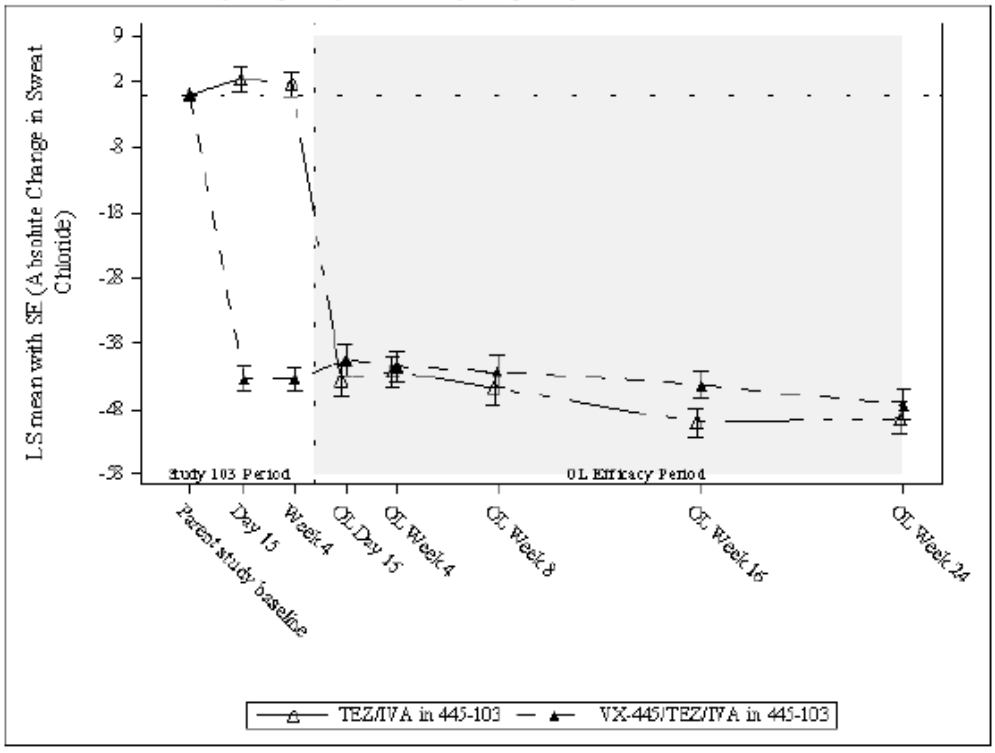
Note: Baseline is the parent study baseline, which was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study.

Figure 11: Study 105 IA2 (F/F Subjects): Absolute Change From Baseline in $ppFEV_1$ (Percentage Points) by Visit, FAS (Study 103)/OL-FAS (Study 105)



Source: IA2 Figure 14.2.1.2
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open label; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

Figure 12: Study 105 IA2 (F/F Subjects): Absolute Change From Baseline in SwCl (mmol/L) by Visit, FAS (Study 103)/OL-FAS (Study 105)



Source: IA2 Figure 14.2.2.2
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open label; SwCl: sweat chloride; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

Analysis performed across trials (meta-analysis)

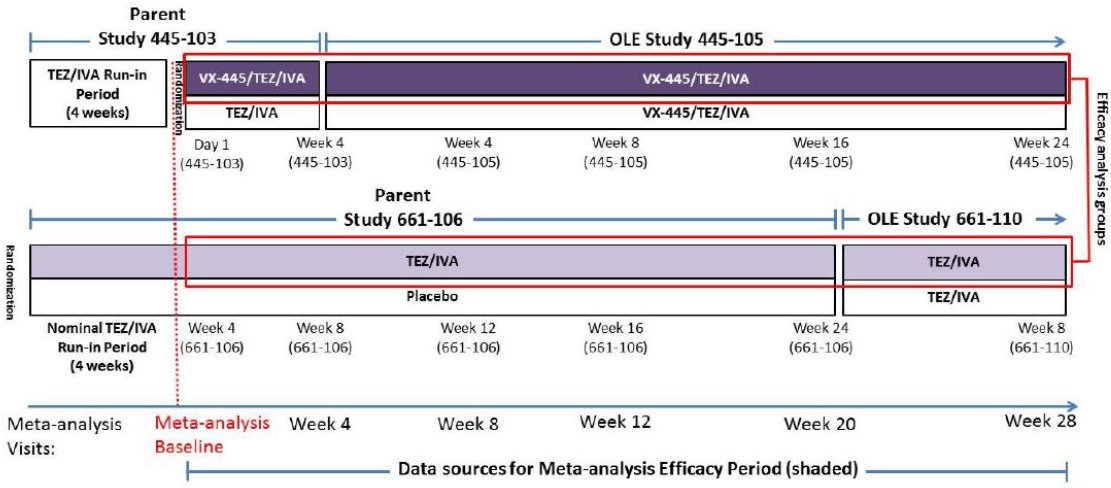
A PDCO-requested cross-study comparison (PIP Study C9 Meta-analysis) was performed to provide at least 24 weeks of comparative efficacy data for the VX-445/TEZ/IVA and TEZ/IVA regimens in F/F subjects.

This cross-study comparison included data from

- 2 studies evaluating VX-445/TEZ/IVA (Studies 103 and OLE 105) and
- 2 studies evaluating TEZ/IVA (Studies 661-106 and OLE 661-110) (used to support the MA for TEZ/IVA in F/F patients).

Baseline in Study 103 was defined after 4 weeks of treatment with TEZ/IVA (TEZ/IVA Run-in Period). In contrast, baseline in Study 661-106 was defined relative to a period without CFTR modulator treatment. To enable a comparison of efficacy, the first 4 weeks of TEZ/IVA treatment in Study 661-106 were considered a nominal TEZ/IVA Run-in Period to match the 4-week TEZ/IVA Run-in Period in Study 103. As a result, baseline values of efficacy endpoints for subjects in Study 661-106 were re-derived as measured at the Week 4 Visit (Figure 13).

Figure 13: Meta-analysis baseline and analysis period for efficacy endpoints



For the efficacy analysis, subjects from the VX-445/TEZ/IVA group in Study 103 and the TEZ/IVA group in Study 106 were compared; the control groups i.e. TEZ/IVA group in Study 103 and the placebo group in Study 106 were not included.

Overall, the demographics and baseline characteristics of subjects in the meta-analysis were very similar between the VX-445/TEZ/IVA patients and the TEZ/IVA patients in terms of age, sex, baseline ppFEV1, and baseline SwCl. In terms of the numbers analysed for the efficacy analysis, 55 were included from the VX-445/TEZ/IVA group and 246 from the TEZ/IVA group in the FAS.

Following the 4-week TEZ/IVA run-in, treatment with VX-445/TEZ/IVA for at least 24 weeks in F/F subjects resulted in robust and clinically meaningful improvements in pulmonary and non-pulmonary endpoints (Table 78). Statistically significant improvements in the VX-445/TEZ/IVA group compared to the TEZ/IVA group were observed for ppFEV1 through 28 weeks of treatment (10.7 percentage points), PEx rate (55% reduction), SwCl (-43.8 mmol/L), CFQ-R RD score (16.5 points), and BMI (1.19 kg/m2). These results provide further support for the superiority of VX 445/TEZ/IVA versus TEZ/IVA.

Responder analysis performed across trials (meta-analysis)

Analysis Methods

Responder analyses for ppFEV1 were conducted using data from 7 pivotal Phase 3 studies of VX-445/TEZ/IVA (Studies 102 and 103), TEZ/IVA (Studies 661-106 and 661-108), or IVA (Studies 770-102, 770-110, and 770-111). An individual subject in Study 102 was classified as a responder based on 2 different thresholds, either ppFEV1 ≥2.5 or ≥5.0 percentage points, if the average of Week 4, Week 8, Week 12, Week 16 and Week 24) is greater than or equal to 2.5 or 5.0, respectively.

Subjects in whom all Week 4, Week 8, Week 12, Week 16 and Week 24 ppFEV1 data were missing were classified as non-responders. An individual subject in Study 103 was classified as a responder in a similar fashion, using absolute change from base in ppFEV1 at Week 4. Because of the difference in study design, the baseline in Study 103 is defined after the 4-week TEZ/IVA run-in; thus, caution should be taken when comparing Study 103 versus other studies. The responders for TEZ/IVA or IVA studies are defined similarly to Study 102, based on the primary ppFEV1 endpoint.

The number and percentage of subjects who had improvements in ppFEV1 of ≥2.5 and ≥5.0 percentage points are summarized in Table 25. To account for differences in study populations, the placebo-adjusted proportion of subjects with improvements in ppFEV1 of ≥2.5 and ≥5.0 percentage points was calculated as the mathematical difference between the percentage of responders in the active treatment group and the placebo group (with the exception of Study 103, which was adjusted using the TEZ/IVA comparator group as there was no placebo group in that study).

Results

These analyses show that a larger proportion of subjects responded to VX445/TEZ/IVA treatment versus placebo in Study 102 than in the pivotal studies for TEZ/IVA and IVA. This is consistent with the substantial magnitude of benefit observed with VX-445/TEZ/IVA treatment.

F/G and F/RF patients treated with VX-445/TEZ/IVA will benefit from fully leveraging both alleles. For the reasons outlined above, a greater proportion of F/G and F/RF patients will respond to VX-445/TEZ/IVA compared to TEZ/IVA and IVA, respectively.

Table 25 Responder Analyses for ppFEV1 in Pivotal VX-445/TEZ/IVA, TEZ/IVA, and IVA studies (FAS)

		Absolute Change in $ppFEV_1$	
Study Number		≥2.5 Percentage Points	≥5.0 Percentage Points
Treatment Group	N	n (%)	n (%)
VX-445/TEZ/IVA			
Study 102 (F/MF)[a]			
VX-445/TEZ/IVA	200	174 (87.0)	155 (77.5)
Placebo	203	46 (22.7)	30 (14.8)
VX-445/TEZ/IVA vs placebo		**64.3%**	**62.7%**
Study 103 (F/F)[b]			
VX-445/TEZ/IVA	55	47 (85.5)	37 (67.3)
TEZ/IVA	52	15 (28.8)	7 (13.5)
VX-445/TEZ/IVA vs TEZ/IVA		**56.7%**	**53.8%**
TEZ/IVA			
Study 661-106 (F/F)[a]			
TEZ/IVA	248	126 (50.8)	81 (32.7)
Placebo	256	52 (20.3)	20 (7.8)
TEZ/IVA vs placebo		**30.5%**	**24.8%**

Study 661-108 (F/RF)[c]			
TEZ/IVA	161	113 (70.2)	86 (53.4)
Placebo	161	41 (25.5)	20 (12.4)
TEZ/IVA vs placebo		**44.7%**	**41.0%**
IVA			
Study 770-102 (G551D)[a]			
IVA	83	75 (90.4)	62 (74.7)
Placebo	78	24 (30.8)	11 (14.1)
IVA vs placebo		**59.6%**	**60.6%**
Study 770-110 (R117H)[a]			
IVA	34	13 (38.2)	13 (38.2)
Placebo	35	8 (22.9)	7 (20.0)
IVA vs placebo		**15.4%**	**18.2%**
Study 770-111 (non-G551D)[d]			
IVA	38	25 (65.8)	19 (50.0)
Placebo	37	3 (8.1)	1 (2.7)
IVA vs placebo		**57.7%**	**47.3%**

Sources: Study 102 Ad hoc Table 14.2.8.49, Study 103 Ad hoc Table 14.2.5.18, Study 661-106 Ad hoc Table 1.1.1, Study 661-108 Ad hoc Table 1.2.1, Study 770-102 Ad hoc Table 2.1.1, Study 770-110 Ad hoc Table 2.1.2, Study 770-111 Ad hoc Table 2.1.3

Notes: All studies evaluated CF subjects ages 12 years and older, with the exception of Studies 770-110 and 770-111 which evaluated CF subjects ages 6 years and older.

[a] Absolute change through Week 24.

[b] Absolute change at Week 4. Baseline in Study 445-103 was established after a 4-week TEZ/IVA run-in period.

[c] Absolute change from baseline to the average of Week 4 and Week 8.

[d] Absolute change through Week 8.

Real World Data

Upon request from CHMP, the MAH provided additional information from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) on F/G and F/RF patients and for F/MF and F/F patients treated with VX-445/TEZ/IVA in the post-authorization setting; this fixed dose combination has been authorised in the US in October 2019 for the initially broader proposed indication in F/any patients.

Data collected by the CFFPR are provided as aggregate data reports only. The MAH did not have access to patient-level data in the registry. Available information has been provided below.

F/MF and F/F

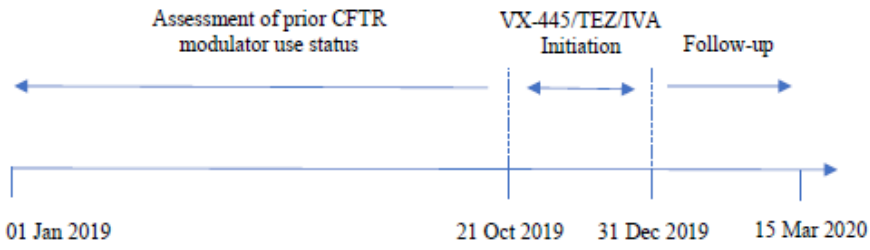
Population

CF patients who met the following criteria were included in the analysis: (1) had a CFFPR record of initiating treatment with VX-445/TEZ/IVA between 21 October 2019 and 31 December 2019, (2) were aged 12 years and older on the date of treatment initiation, (3) had a F/MF or F/F genotype, and (4) had ppFEV1 assessments available both within 90 days before (baseline) and any time after (follow-up) treatment initiation through 15 March 2020. F/MF subjects included in this analysis had MF mutations that were defined consistently with those in Study 102.

The analysis population is summarized in

Figure 14.

Figure 14: Patient population included in the CFFPR analyses



Individual patient-level genotype data for the analysis population were not available in this data cut.

From 21 October 2019 through 31 December 2019, a total of 1,448 F/MF and 3,178 F/F patients had a record of VX-445/TEZ/IVA treatment initiation in CFFPR; of those patients, 995 (68.7%) and 2,200 (69.2%) respectively had lung function measurements available both at baseline and follow-up and were included in these analyses.

The F/MF patients had a mean age of 26.3 years and mean treatment duration of 65.6 days. The F/F patients had a mean age of 26.7 years and mean treatment duration of 65.4 days.

Outcomes and Data Analysis

Improvement in lung function, as assessed by ppFEV1, was used to determine the treatment effect with VX-445/TEZ/IVA. Other efficacy parameters (e.g., SwCl, CFQ-R) are not routinely collected in the clinical practice and/or not captured in the CFFPR and thus were not evaluated in this analysis.

The most recent measurement obtained within 90 days before VX-445/TEZ/IVA treatment initiation served as the baseline value. The last measurement available in the period following therapy initiation on or before 15 March 2020 served as the follow-up value. The change in ppFEV1 was calculated as a difference between the follow-up and baseline value for each patient, and data were summarized for F/MF and F/F subgroups using summary statistics (mean, standard deviation [SD], 95% confidence intervals [CI]).

Patients who were initiated on VX-445/TEZ/IVA treatment in 2019 were followed from the date of VX-445/TEZ/IVA treatment initiation through 15 March 2020. Treatment duration was calculated for each patient as the difference in days between the date of treatment initiation and the date of the last available post-treatment ppFEV1. Mean treatment durations were calculated for the F/MF and F/F subgroups separately.

Mean patient age at the time of VX-445/TEZ/IVA treatment initiation was summarized for the F/MF and F/F subgroups separately.

Recent use of CFTR modulator therapy prior to VX-445/TEZ/IVA treatment initiation was defined as any record in the registry of exposure to CFTR modulator therapy in 2019 prior to the VX-445/TEZ/IVA treatment initiation date; the actual CFTR modulator therapy used prior to VX-445/TEZ/IVA was not available in this data cut. Precise start and stop dates for LUM/IVA and TEZ/IVA are not available in the CFFPR and the exposure status was determined based on the presence or absence of the treatment record at each patient encounter. In 2019, in anticipation of VX-445/TEZ/IVA, CFFPR introduced a new data collection element to capture the approximate date the patient started taking therapy, which allowed more precise estimation of VX-445/TEZ/IVA initiation date in this analysis.

Results

As expected, based on the market availability of CFTR modulators indicated for patients with F/F genotype (LUM/IVA and TEZ/IVA), the vast majority of the F/F patients included in this analysis were receiving CFTR modulator therapy prior to initiating VX-445/TEZ/IVA treatment (91.5% were exposed

to at least one other CFTR modulator in 2019). In contrast, consistent with the lack of approved CFTR modulator therapy for the F/MF population, only 2.9% of F/MF patients had a record of receiving CFTR modulator therapy prior to initiating VX-445/TEZ/IVA treatment.

Mean baseline ppFEV1 values were 65.7 for the F/MF patients and 65.8 for the F/F patients. An improvement in ppFEV1 from baseline was observed for both genotype groups: mean of 10.9 percentage points (95% CI: 10.0, 11.8) for the F/MF patients and 9.0 percentage points (95% CI: 8.6, 9.4) for the F/F patients (Table 26).

The data from CFFPR in F/MF and F/F patients demonstrate the transformational benefit of VX-445/TEZ/IVA in these patients. The results are consistent with results from the pivotal clinical studies in F/MF and F/F (Table 26).

Table 26 Comparison of CFFPR data with the result of the pivotal clinical studies for F/MF and F/F patients

	CFFPR Data			Pivotal Clinical Studies (Within-group Analysis)			
Genotype	Patients n	Change in $ppFEV_1$ Mean (SD)	95% CI for Change in $ppFEV_1$ [b]	Timepoint	Patients N [c]	Change in $ppFEV_1$ Mean [d]	95% CI for Change in $ppFEV_1$ [d]
F/MF	995	10.9 (15.1)	(10.0, 11.8)	Week 4	200	13.5	(12.3, 14.7)
				Week 24	200	13.9	(12.8, 15.0)
F/F	2200	9.0 (10.2)	(8.6, 9.4)	Week 4	55	10.4	(8.6, 12.2)

Source: data on file from CFFPR and Module 2.5
Note: CFFPR data are from F/MF and F/F patients who initiated treatment with VX-445/TEZ/IVA between 21 October 2019 and 31 December 2019. F/MF subjects were evaluated in Study 102. F/F subjects were evaluated in Study 103.
[a] Post-treatment $ppFEV_1$ data examined through 15 March 2020
[b] 95% CI was calculated by Vertex based on one sample t test.
[c] Number of patients represents those included in the Full Analysis Set.
[d] Model-based LS means and 95% CIs are presented.

F/RF and F/G

Population

CF patients who met the following criteria were included in the analysis: (1) had a CFFPR record of initiating treatment with VX-445/TEZ/IVA between 21 October 2019 and 31 December 2019, (2) were aged 12 years and older on the date of treatment initiation, (3) had a F/G or F/RF genotype, and (4) had ppFEV1 assessments available both within 90 days before (baseline) and any time after (follow-up) treatment initiation through 15 March 2020. The gating and RF mutations included were consistent with the eligible population in Study 104, and reflect the gating mutations for which Kalydeco is indicated and the RF mutations for which both Kalydeco and Symdeko are indicated in the US.

Gating mutations eligible for inclusion in the analyses were *G1069R, G1244E, G1349D, G178R, G551D, G551S, R1070Q, R117H, S1251N, S1255P, S549N, or S549R*.

RF mutations eligible for inclusion in the analyses were *2789+5G->A, 3272-26A->G, 3849+10kbC->T, 711+3A->G, A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, or S977F*.

Individual patient-level genotype data for the analysis population were not available in this data cut. From 21 October 2019 through 31 December 2019, a total of 521 F/G or F/RF patients had a record of VX-445/TEZ/IVA treatment initiation in CFFPR. Of these patients, 297 patients (57%) had lung function

measurements available both at baseline and follow-up and were included in these analyses. Their mean treatment duration was 63.4 days.

Results

There were 136 F/G patients who had a mean age of 32.3 years and a mean treatment duration of 62.8 days. There were 161 F/RF patients who had a mean age of 40.3 years and a mean treatment duration of 63.8 days. As expected, based on the market availability of CFTR modulators indicated for patients with gating (IVA) and RF (IVA, TEZ/IVA) mutations, the vast majority of the F/G and F/RF patients included in this analysis were receiving CFTR modulator therapy prior to initiating VX-445/TEZ/IVA treatment (97.8% of F/G patients and 89.4% F/RF patients were exposed to at least one other CFTR modulator in 2019).

Mean baseline ppFEV1 values were 69.0 for the F/G patients and 66.6 for the F/RF patients. An improvement in ppFEV1 from baseline was observed for both genotype groups: mean of 4.3 percentage points (95% CI: 2.7, 5.9) for the F/G patients, and 2.7 percentage points (95% CI: 1.7, 3.7) for the F/RF patients (Table 27).

Table 27 CFFPR data for F/G and F/RF patients

Subgroup	Patients n	Pre-VX-445/TEZ/IVA ppFEV$_1$ Mean (SD)	Post-VX-445/TEZ/IVA ppFEV$_1$ [a] Mean (SD)	Change in ppFEV$_1$ Mean (SD)	95% CI for Change in ppFEV$_1$ [b]
F/G	136	69.0 (26.1)	73.3 (25.2)	+4.3 (9.6)	(2.7, 5.9)
F/RF	161	66.6 (25.1)	69.3 (24.8)	+2.7 (6.6)	(1.7, 3.7)

Source: data on file from CFFPR
[a] Post-treatment ppFEV$_1$ data examined through 15 March 2020
[b] 95% CI was calculated by Vertex based on one sample t test.

2.4.3. Discussion on clinical efficacy

In this variation, the MAH initially applied for the inclusion of the following indication in section 4.1. of Kalydeco SmPC:

"Kalydeco tablets are indicated in a combination regimen with elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene."

The initially claimed indication includes patients with *F508del* and a so called 'minimal function' mutation i.e. F/MF genotypes, a group which has not responded to the currently approved CFTR modulating options. It also includes patients with the F/F genotype, as well as patients with F/G (*F508del* with a gating mutation) as well as F/RF (*F508del* with a residual function mutation). For some patients, e.g. F/F patients and those patients with F/RF and F/G genotypes who currently have approved therapies, this triple therapy could replace the existing therapy. The MAH considered that the triple combination targets and exerts its effect entirely by correcting the CFTR defect caused by the F508del allele, regardless of what second allele is present, and sees this as a new treatment approach. However, as discussed below, the *F508del*-only paradigm has not been fully substantiated, and therefore robust clinical data in F/G and F/RF populations are needed to support the inclusion of these patients in the indication. The indication was therefore restricted, in line with Kaftrio indication

The discussion below outlines the rationale for the indication of Kalydeco in combination with Kaftrio as discussed in the Kaftrio CHMP AR (EMEA/H/C/005269/0000).

Design and conduct of the studies

Dosing of VX-445 was investigated in one Phase 1/2 study, Study 001. In healthy volunteers, single and multiple ascending doses were tested ranging from 20mg – 340 mg per dose VX-445. In patients, different doses (50mg, 100mg and 200mg) daily were tested in F/MF subjects. In F/F patients, only the final 200mg dose was tested.

Efficacy and safety have been evaluated in three phase 3 studies in CF patients aged 12 years and older. Study **102** in subjects heterozygous for *F508del* and a minimal function mutation (F/MF) and study **103** in subjects homozygous for *F508del* (F/F) are the core efficacy studies. These studies were randomised double-blind, controlled multicentre studies. Study **105** was designed to support persistence of efficacy and long-term safety. Results are currently submitted as an interim analysis (IA2).

Furthermore, a cross-study comparison "**the Meta-analysis**", requested by the PDCO, was performed in which the results of Studies 103 and 105 and the phase 3 studies for Symkevi (study 106 and 110) were pooled and compared.

Upon request by CHMP, **real world data** (from the US Cystic Fibrosis Foundation Patient Registry, CFFPR) from a post-authorization setting were also provided.

Comparator
In the **F/MF** patient population (study 001 and 102), placebo was used as the comparator. This is considered to be an acceptable treatment arm because no other approved regimens have shown clinical efficacy in the F/MF populations, justifying the absence of TEZ/IVA or LUM/IVA arm.

In the **F/F** population (study 001 and 103), TEZ/IVA was used as the comparator, in patients already treated with TEZ/IVA. This is also considered an acceptable treatment arm because it is the best approved regimen in the F/F population. However, the choice of only placebo in F/MF or TEZ/IVA in F/F as a comparator can be questioned. The added effect of VX-445/TEZ/IVA over VX-445 monotherapy or VX-445/IVA is solely based on *in vitro* and mechanistic data. These data suggest that the triple combination provides additional benefit over all mono/dual therapies in both F/MF and F/F cells. It also indicates that TEZ and VX-445 can bind simultaneously to the CFTR protein (only wild-type CFTR tested). Nevertheless, clinical evaluation of VX-445 monotherapy and VX-445/IVA compared with the TC, was strongly recommended in Scientific Advices given by CHMP and national authorities. This is also in line with the Guideline for Fixed Dose Combinations (EMA/CHMP/158268/2017) which states that "*clinical trials demonstrating efficacy/safety of the new active substance as monotherapy"* should be performed. While information on the safety of VX-445 can be derived from the currently provided and previously submitted clinical studies performed with placebo and TEZ/IVA; clinical efficacy data would be required, in particular, compared to the VX-445/IVA combination. However, it is considered that *in vitro* results, confirming the added benefit of the combination of two correctors (VX-445 and TEZ) over VX-445 alone provides valuable information and demonstrates that both correctors VX-445 and TEZ are required in combination with a potentiator (IVA).

The HBE cells used to generate in vitro data can be regarded as a relevant model system to study the pharmacological action of CFTR modulators. Three donors with an F/F genotype were analysed and 4 donors with an F/MF genotype (2x *G452X* (non-sense); *3905InsT* (small insertion); *E585X* (non-sense). In study 102; 65, 5 and 1 patients with this genotype were included respectively.

The in vitro data suggest that the triple combination does provide a benefit over all mono and dual combination of VX-445, TEZ and IVA in all tested donors.

Uncertainties remain on the contribution of all components, as not all combination are tested in a clinical setting and the FDC guideline is not followed. Nevertheless, the *in vitro* data, the highly

clinically relevant benefit and well-tolerated safety profile of the VX-445/TEZ/IVA in the F/MF and F/F population are considered relevant enough to outweigh these uncertainties on the contribution of the mono-components in a clinical setting.

Duration

The duration of the dose finding study 001 of 28 days is acceptable for the objective. The 24-week treatment period of pivotal study 102 is in line with the EMA guideline on CF and CHMP's scientific advice (SA) received. However, the 4-week treatment period of pivotal study 103 is not in line with guidelines and SA, thus, robust conclusion cannot be drawn on the sustainability of the effect of the triple combination. The MAH considered the short duration acceptable as a sustained benefit from day 15 towards week 24 has always been shown in studies with other modifiers. Although this has indeed been observed, the results from the in between time were fluctuating and not completely stable. Furthermore, important efficacy parameters such as exacerbations and BMI cannot be reliably measured in a study with a duration of 4 weeks. Therefore, a 4-week study is too short to establish a long-term clinical benefit. The open label extension study (Study 105) provides further data on the maintenance of efficacy and long-term safety, which is considered acceptable.

Inclusion and exclusion criteria

The in-and exclusion criteria for the dose-response study 001, and pivotal trials 102 and 103 were largely similar, except for age (dose response only adult patients, pivotal also adolescents) and the genotype mutations. Patients had to have FEV1 ≥40% and ≤ 90% and stable CF. Diagnosis of CF was confirmed by the investigator. Only a limited number of patients with a SwCl of < 60 mmol/L were included in the trial 102 (and sensitivity analysis without these patients show consistent results). No patients with a SwCl of < 60 mmol/L at baseline were included in study 103.

F/F and F/MF population

In study 102, the definition of an MF mutation was quite unusual. The MAH defines an MF mutation as follows: (1) no CFTR protein or (2) a CFTR protein that is not responsive to IVA and TEZ/IVA *in vitro*. A mutation was considered an MF mutation if it meets at least 1 of the following 2 criteria:
(1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein). A list of eligible MF mutations was specified.
(2) *in vitro* testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA, and evidence of clinical severity on a population basis (as reported in large patient registries).

- *In vitro* baseline chloride transport of < 10% of WT CFTR and increase of chloride transport <10% over baseline after TEZ, IVA or TEZ/IVA.
- Clinical severity (CFTR2 patients registry) → average sweat chloride >86 mmol/L and prevalence of pancreatic insufficiently (PI) > 50%.

With regard to criterion (1), the pre-specified list contains mutations that are likely to have no CFTR translated protein. The idea of the MAH that VX-445/TEZ/IVA only requires one F508del allele is based on the fact that the (included) MF mutations in trial 102 have no protein and therefore the effect seen has to be caused by the F508del allele. Although plausible, it is possible that some of the MF mutants may have a minor contribution to the CFTR-mediated chloride transport upon treatment with VX-445/TEZ/IVA.

With regard to criterion (2), the 10% cut-off seems acceptable as it has been used and justified in previous procedures. The mutations were tested for non-responsiveness to VX-445/TEZ/IVA. In FRT cells, 8 mutations (*3199del16, A559T, I507del, L467P, N1303K, R1066C, R560T, V520F*) did not respond to VX-445/TEZ/IVA treatment, while 4 mutations (*G85E, M1101K, L1077P and R347P*) did show responsiveness. However, the inclusion and responsiveness data are based on the assumption that *in vitro* data do correlate with *in vivo* data, while an IVIVC is not established.

Therefore, the results from the patients included based on criterion (1), which is 78% of the patients, is mainly considered of value (provided as an ad-hoc analysis). The efficacy in this subset and in genotype subgroups could be used to draw conclusions on the acceptability of the "new paradigm" i.e. only one single *F508del* allele is required. The totality of evidence generated in the pivotal clinical studies could be considered to draw a conclusion on whether the *F508del* allele is the main target of action (see further discussion below).

In terms of F/F patients entering **Study 103** some patients may have already been on therapy at the time of screening, and indeed could continue therapy right up to the start of the TEZ/IVA run in, while others may have been naïve to Vertex CFTR modulators (of note, those on non-Vertex CFTR modulators had a wash out prior to screening). Stratification according to ppFEV1 was applied on the ppFEV1 measurements taken after at least 13 days of TEZ/IVA run-in, rather than the screening ppFEV1 values. A subgroup analysis for Vertex CFTR modulator naïve versus treatment-experienced patients indicates that the magnitude of the observed treatment effect (LS mean 7.8%, 95% CI (4.8, 10.8)) for CFTR modulator experienced patients is less than that for CFTR modulator naïve patients (LS mean 13.2%, 95% CI (8.5, 17.9). Overall various subgroup analyses do not suggest a differential treatment effect for CFTR-modulator naïve and CFTR-modulator experienced patients. However, subjects who were CFTR modulator naïve had a lower mean baseline ppFEV1 value (58.5 for the VX-445/TEZ/IVA group and 57.2 for the TEZ/IVA group) than subjects who were CFTR modulator experienced (63.8 for the VX-445/TEZ/IVA group and 61.8 for the TEZ/IVA group). Although the small sample size in these subgroups is acknowledged, comparison of the week 4 and week 8 ppFEV1 values across these four subgroups suggests that the screening period of 4 weeks may not have been sufficient for CFTR-modulator naïve patients randomized to TEZ/IVA to derive the full benefit of this treatment by time of baseline ppFEV1 assessment. Consequently, it is considered that the magnitude of the treatment effect of VX-445/TEZ/IVA vs TEZ/IVA in the overall study 102 population may be overestimated and that the treatment effect estimate obtained in the CFTR-modulator experienced patients is relevant to prescribers (LS mean 7.8%, 95% CI (4.8,10.8)).

Study **105** is an extension study and enrolled subjects who participated in study 102 and 103.

Endpoints

The parameters ppFEV1 and SwCl endpoints were used in the dose response study 001. These parameters are acceptable endpoints to define the Dose-Response relationship.

For the pivotal studies 102 and 103, the primary endpoint was an absolute change in LS mean ppFEV1 (through week 24 and at week 4, for study 102 and 103 respectively). ppFEV1 is the advocated primary endpoint in EMA's guideline on CF (CHMP/EWP/9147/08). The key secondary efficacy endpoints in study 102 (number of pulmonary exacerbations, absolute change in SwCl, absolute change in CFQ-R RD Score and absolute change in BMI) and study 103 (absolute change in SwCl and absolute change in CFQ-R RD Score) are all accepted endpoints in clinical trials on CF. The same endpoints were used in study 105.

Efficacy on other organs could have been explored by analysing faecal elastase-1, plasma IRT, bile acids C4 and FGF. However, such data were not collected as the included subjects are likely to have progressive damage to their exocrine pancreas that is irreversible.

Statistical Analyses

For study 102, the primary analysis was performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at Week 4, Week 8, Week 12, Week 16, and Week 24 as the dependent variable. The model included treatment group, visit, and treatment by visit interaction as fixed effects, with continuous baseline ppFEV1, age at screening (<18 versus ≥18 years of age) and

sex (male versus female) as covariates. Type I error was controlled through a hierarchical testing-procedure.

For study 103, a MMRM was also used, but with Day 15 and Week 4 as the dependent variable and with continuous baseline ppFEV1 and age at screening (<18 versus ≥18 years of age) as covariates. The use of a MMRM for the evaluation of the primary endpoint in both studies is acceptable. The analyses used to examine the secondary endpoints are also acceptable.

In extension study 105, a MMRM was also used to estimate the change from baseline in ppFEV1 at each time point.

In both pivotal studies, a sensitivity analysis was performed for the evaluation of the primary endpoints. This sensitivity analysis was based on the classification of patients with missing data into a number of missing categories and may not have been sufficiently sensitive to examine departures from the missing at random assumption. However, the rate of missing data is low.

Efficacy and additional analyses

Dose regimen

Adults and Adolescents

The intended dosing regimen (VX-445 200 mg qd, TEZ 100 mg qd and IVA 150 mg q12h), is acceptable, and therefore 150 mg Ivacaftor was used in the pivotal studies as an evening dose in combination with Kaftrio, administered in the morning.

The posology for special population is addressed later in this section.

Pivotal studies

*CF patients 12 years or older with the **F/MF** genotype (study 102)*

In pivotal study 102, the demographic and baseline characteristics were balanced between the two treatment groups. In terms of the F/MF genotypes represented in the clinical study, across the 403 F/MF subjects in the FAS, 79 different MF mutations have been represented. 314/403 patients had Class I (i.e. no CFTR) mutation; in total 67 Class I mutations were recruited. In terms of mutations that are not Class I, (i.e. qualified under Criterion 2), 12 MF mutation types were recruited (missense or in frame deletion mutations) in 89 patients. Due to the genetic variability of CF as a disease, it is understood that not all genotypes will be able to be tested.

The inclusion of patients with ppFEV1 <40 (34/403) did not comply with the inclusion criteria. The inclusion criterion pertaining to screening ppFEV1 was met in all enrolled subjects in Study 102, but the ppFEV1 decreased at their baseline study visit.

Three concomitant antibiotic treatments were used more often in the placebo group (Tobramycin: 55.7% vs 39%; Ciprofloxacin: 36% vs 16%; Sulfamethoxazole and trimethoprim: 26.1% vs 17.0%). This difference can be attributed to the imbalance in the occurrence of pulmonary exacerbations (PEx) (numerically higher in the placebo group). These antibiotic usage differences are a consequence of the effectiveness of the VX-445/TEZ/IVA regimen.

Missing data for the repeated measurements data was not an issue (less than 10%).

For the primary endpoint, the LS mean treatment difference in absolute change in ppFEV1 through week 24 between the VX-445TEZ/IVA and placebo groups was 14.3% (95% CI: 12.7 – 15.8; p<0.0001) in favour of the triple combination. The obtained difference was above the predefined threshold (5.0%) and considered clinically relevant (Report of the workshop on endpoints for cystic fibrosis clinical trials (EMA/769571/2012)). Approximately 80% patients treated with the TC have a

benefit of ppFEV1 >5%, compared to 15% in the placebo group. The result of the sensitivity analysis, a MMRM based on multiple imputations (MIs), was consistent with the primary analysis.

The key secondary endpoint, absolute change in ppFEV1 in 4 weeks, was in line with the results of the primary endpoint at 24 weeks (13.7 %; P<0.0001; 95% CI: 12.0, 15.3). This suggests a stable improvement from 4 weeks on.

For the key secondary endpoints pulmonary exacerbations, the rate ratio was 0.37 (95% CI: 0.25 – 0.55, p<0.0001) in favour of VX-445/TEZ/IVA. This is a reduction of 63%, which is considered clinically relevant. Also, the reductions in exacerbations requiring hospitalization and/or IV antibiotic treatment were statistically and clinically significant. The hazard ratio for time-to-first pulmonary exacerbation was also in favour of the triple combination (HR: 0.34; 95% CI 0.22, 0.52; p<0.0001).

For the key secondary endpoint, changes in SwCl from baseline, the stable reduction of -41.8 mmol/L (95% CI: -44.4 to -39.3; p< 0.0001) through week 24 compared to placebo is considered clinically relevant (MCID: -10 mmol/L). Approximately 95% of the patients treated with the TC had clinically relevant benefit, compared to only 5% in the placebo group.

Also, a key secondary endpoint, change in CRQ-R RD score, improved significantly in the TC arm compared to the placebo arm (20.2 points; 95% CI 17.5,23.0; p<0.0001). With an MCID of 4 points, this increase in considered clinically relevant, all other CFQ-R domains indicated also an improvement with the TC compared to placebo, consistent with the results of the key secondary endpoint absolute change in BMI (1.04 (95% CI: 0.85, 1.23; p<0.0001) compared to placebo).

At baseline, median BMI baseline was 20.80 kg/m2 (min, max: 14.42, 33.80) in the placebo group and 21.36 (15.01, 30.86) in the TC group. In total, study 102 recruited 50 overweight patients, and 17 undernourished patients. Therefore, there were an unknown number of underweight subjects as well as of overweight/obese patients. An analysis of BMI was provided for undernourished and overweight subjects according to the WHO thresholds, both overweight and underweight patients treated with VX-445/TEZ/IVA showed gains in BMI consistent with the overall population.

Consistent and significant benefits in ppFEV1 favouring VX-445/TEZ/IVA were observed across all prespecified subgroups: age, sex, baseline lung function, region, *P. aeruginosa* infection, and baseline use of common CF medications.

An ad-hoc subgroup analysis was performed on patients included based on genetic criterion 1 (likely to have no CFTR protein translated) and on criterion 2 (missense not responding the TEZ and/or IVA *in vitro*). Class 1 (MF) mutant patients show an absolute change from baseline in ppFEV1 of 14.8% comparing the triple combination with placebo. The missense mutant patients showed a difference in ppFEV1 of 12.9%. Furthermore, for the criterion 1 mutations, a subdivision was made for Nonsense mutations, Canonical splice mutations and insertions/deletions leading to a frameshift. For missense and in-frame deletions (criterion 2) a subdivision was made for mutations that were responsive or not to the triple therapy. The outcomes of these analyses were similar to the overall study outcome.

Within the IA2 from study 105, the efficacy data were presented for patients from parent study 102. These data show that the positive treatment effect continues to be maintained with continued treatment. In general, the data indicates that for MF patients from the "placebo" group, treatment with VX-445/TEZ/IVA results in a similar benefit for all efficacy parameters when compared to the group that received the triple combination in study 102 already. When comparing the data from week 24 and week 48 for the patients that received the triple combination in study 102 already, all the efficacy parameters still seem to improve (slightly). Outcomes of subgroup analyses for FEV1 and SwCL performed for the different MF genotypes were similar to the overall study outcome.

*CF patients 12 years or older with the **F/F** genotype (study 103/105)*
In pivotal study 103, the demographic and baseline characteristics were balanced between the two treatment groups. Missing data for the repeated measurements data was not an issue (less than 10%).

For the primary endpoint, the LS mean treatment difference in absolute change in ppFEV1 at week 4 between the VX-445TEZ/IVA and TEZ/IVA groups was 10.0% (95% CI: 7.4 – 12.6; p<0.0001) in favour of the triple combination. The obtained difference was above the predefined threshold (5.0%) and considered clinically relevant. Approximately 70% patients treated with the TC have a benefit of ppFEV1 >5%, compared to 13% in the TEZ/IVA group.

For the key secondary endpoint, change in SwCl from baseline, a positive effect is observed after treatment with VX-445/TEZ/IVA compared to TEZ/IVA. A stable reduction of -45.1 mmol/L (95% CI: -50.1 to -40.1; p< 0.0001) at week 4 is considered clinically relevant. Approximately 95% of the patients had a clinically relevant reduction in SwCl, when treated with the triple combination.
Change in CRQ-R RD score, key secondary endpoint, also improved significantly in the TC arm compared to the TEZ/IVA arm (17.4 points; 95% CI 11.8,23.0; p<0.0001). Also, all other CFQ-R domains indicated an improvement with the TC compared to TEZ/IVA.

Although no robust conclusion can be drawn, ad hoc analyses on BMI and weight also seem to demonstrate the beneficial effect of the TC over TEZ/IVA.

Consistent benefits in ppFEV1 favouring VX-445/TEZ/IVA were observed across all prespecified subgroups: age, sex, baseline lung function, region, *P. aeruginosa* infection, and baseline use of common CF medications.

Extension study 105

Because of the short (4 week) duration of study 103, also the result from the extension study 105 were analysed to identify whether the effects seen at 4 weeks, remained stable up to 24 weeks of treatment. All patients rolled over to study 105, in which the patients from the TEZ/IVA group also received the triple combination.

The results for the change in ppFEV1, SwCl and CFQ-R RD showed maintenance of response when treated with VX-445/TEZ/IVA. Subjects treated with the TC in the parent study continued to have a similar benefit at 4 weeks and through 24 weeks of treatment, respectively (ppFEV1: 10.4 vs 10.9 percentage points; SwCL: -43.4 vs -47.2 mmol/L; CFQ-R RD: 16 vs 14.3 points).

With a longer follow-up, data for pulmonary exacerbations and the nutritional status also became available.

For the number of PEx, an estimated event rate per year of 0.30 (95% CI: 0.18-0.48) and a probability of event-free survival of 0.859 (95% CI: 0.777-0.912) was anticipated. For this endpoint, no control-group, or event rate at baseline was present. Therefore, the benefit over TEZ/IVA is difficult to determine. When comparing the observed PEx data for study 103/105 to the data from the VX-445/TEZ/IVA group in study 102 (event rate per year 0.37 (0.25, 0.55); probability of event-free survival 0.842 (0.783, 0.886), this is considered similar. Therefore, the presented exacerbation results for F/F patients from study 105, seem supportive for the benefit seen with the TC.
With regard to the nutritional status, a benefit compared to baseline was observed for all parameters (change in BMI, BMI z-score and body weight).

Overall, the efficacy results from the F/F patients in study 105, confirmed that also in this patient population a long-term benefit can be seen after treatment with VX-445/TEZ/IVA. These results overcome the uncertainties that went along with the 4-week study duration of study 103.

Cross study comparison/Responder analysis

In addition, a responder analysis was performed for the 7 pivotal Phase 3 studies of VX-445/TEZ/IVA (Studies 102 and 103), TEZ/IVA (Studies 661-106 and 661-108), or IVA (Studies 770-102, 770-110, and 770-111). The comparison between the placebo controlled studies in patients with at least one *F508del* allele (study 661-108 (F/RF), study 661-106 (F/F) and study 102 (F/MF) could suggest that at least an additional 20% of patients will have a clinically relevant response to VX-445/TEZ/IVA compared to TEZ/IVA. However, this would be a useful comparison if the F/any paradigm would be well demonstrated (which currently is not), and therefore by extension that it could be accepted that all genotypes with one F can be assumed to respond sufficiently.

Moreover, the comparisons are based on cross-study comparisons with different populations, which introduces uncertainties and these comparisons cannot be considered as additional evidence for the F/any paradigm or to support extrapolation of findings in the F/MF population to the F/G and F/RF populations. The CHMP considered that the F/any hypothesis has not been conclusively demonstrated. As such, the F/G and F/RF require their own demonstration of clinical efficacy and safety. It is thus considered that these comparisons while interesting, do not obviate the need for robust, comparative, clinical data in F/G and F/RF patients from clinical studies.

Real world clinical data

Upon request by CHMP, the MAH provided real world data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) for **F/RF** and **F/G** and also F/F and F/MF patients treated with VX-445/TEZ/IVA.

F/RF and F/G patients who started with VX-445/TEZ/IVA therapy between 21 October 2019 and 31 December 2019 (n=521), who had a lung function measurement at baseline and follow-up (n=297, 57%) were included in the analyses. Only ppFEV1 values were provided, as other efficacy parameters are not routinely measured. The registry data from the F/MF and F/F patient population showed results in line with the effects observed in studies 102 and 103.

The U.S. CFFPR data presented are in itself limited and not sufficiently detailed, and as such raised several questions such as the exact modulator therapy used, the duration of use which is not known, as well as included specific genotypes and individual patient efficacy data which are not presented. Unavailability of such information is inherent to registry data but does introduce uncertainties. It can also be questioned whether the patients in the analysis set can be considered sufficiently representative of the overall F/G and F/RF populations to allow conclusions in such patient populations.

Based on the available data, improvements in ppFEV1 were seen in the 136 F/G and 161 F/RF populations of 4.3% and 2.7% respectively. These improvements are observed on top of approved therapies as at least 90% of the patients were exposed to at least one other *CFTR* modulator. However, it appeared that patients only needed record of exposure to *CFTR* modulators in 2019; hence it is possible that some patients may not have been current users of *CFTR* modulators at the time of starting triple therapy, and as such the 'experienced' figures presented may be an overestimation.

Taking into account the limitations and questions arising from the data registry, the magnitude of the additional response from treatment with VX445/TEZ/IVA over prior *CFTR* therapies is limited. It is unexpected that the F/G group had greater efficacy compared to the F/RF population. Indeed, in view of the limited efficacy observed in clinical trials for F/RFs patients treated with TEZ/IVA compared with patients with G/any mutations treated with IVA, it would be considered that F/RF group should have had more potential for improvement with VX445/TEZ/IVA by treating the F allele.

It is however agreed that effect size estimates in these real-world analyses are not directly comparable to results from a clinical study in which data are collected in a controlled setting. For example, the

ppFEV1 data from the pivotal clinical studies were captured and analysed after a 4-week treatment duration (Studies 102 and 103) and a 24-week treatment duration (Study 102). In contrast, ppFEV1 measurements used in this analysis of CFFPR data were captured at different time points following initiation of VX-445/TEZ/IVA treatment reflecting the real-world nature of data collection in routine clinical practice (from <28 days to over 90 days, with the mean exposure duration of 65.6 days for F/MF patients and 65.4 days for F/F patients, as noted above). Additionally, spirometry data collected in the CFFPR has greater variability because the assessment is performed at a local site using local equipment compared to the standardized equipment and protocols used in a clinical study.

The CHMP considered that the registry data do not obviate the need for robust, comparative, clinical efficacy and safety data in F/G and F/RF patients from randomized controlled clinical studies.

In conclusion, the cross-study comparison, responder analysis and the registry data on its own without the ongoing clinical trial (study 104) data in F/G and F/RF mutations do not sufficiently support the added benefit over approved modulator therapies. Therefore, the CHMP considered that the efficacy has been demonstrated only in patients with F/F and F/MF mutations where randomized clinical trial data are available.

Thus, the indication for Kalydeco in combination with Kaftrio was restricted to the patients with F/F and F/MF mutations only, reflecting the agreed indication for Kaftrio.

Regarding the posology, it has been correctly reflected in 4.2, the information related to special population has also been updated, in particular hepatic impairment (sections 4.2 and 4.4 of the SmPC), The use of Kalydeco in combination with Kaftrio in case of concomitant use with moderate or strong CYP3A4 is also amended in section 4.2.

2.4.4. Conclusions on the clinical efficacy

The final indication granted by CHMP is as follows:

'Kalydeco tablets are indicated in a combination regimen with ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for F508del mutation in the CFTR gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.'

Sections 4.2, 4.4 have been amended and results have been added in section 5.1.

2.5. Clinical safety

Introduction

The safety data submitted in this application are identical to the Kaftrio application (EMEA/H/C/005269/0000). The data are provided below.

The clinical safety database included 10 clinical studies with VX-445 as a monotherapy or as part of a TC regimen, including 5 completed Phase 1 studies (Study 002 (OC DDI), 003 (ADME), 005 (FDC BA), 006(DDI) and 009 (QT/QTc), 1 completed Phase 1/2 study (Study 001), 2 completed Phase 3 studies (102 and 103), and 2 ongoing Phase 3 studies (study 105 - long term safety and study and 106 - safety and PK).

Core Safety Analyses

The core safety analyses in CF subjects evaluated data from Study 102, Study 103, and an interim analysis (IA2) of the open-label extension Study 105.

Safety data from Studies 102 and 103 were not pooled in the core safety analysis because of the substantial differences in the designs of the 2 studies. These differences involve especially treatment duration, use of different comparator groups i.e. a placebo group in Study 102 and an active comparator in study 103. Because of these differences, pooling the data could confound the comparison between VX-445/TEZ/IVA and placebo in Study 102.

- The Study 102 Safety Set contains all subjects who received at least 1 dose of study drug.
- The Study 103 Safety Set for the Treatment Period (hereafter the Study 103 Safety Set) includes all subjects who received at least 1 dose of study drug in the Study 103 Treatment Period (i.e., does not include subjects who were only dosed in the TEZ/IVA Run-in Period).
- The Study 105 Safety Set includes all subjects who received at least 1 dose of study drug in Study 105.
- The Cumulative Safety Set includes all subjects who received at least 1 dose of VX-445/TEZ/IVA during the parent Studies 102 or 103 and/or during Study 105.
    - Selected safety analyses were performed for the subset of subjects in the Cumulative Safety Set who received ≥48 weeks of treatment with VX-445/TEZ/IVA.

In addition, supportive safety analyses are submitted for various doses of VX-445 and multiple treatment regimens (different TC regimens) in study 001 and ongoing Study 106 in CF subjects 6 through 11 years of age.

Patient exposure

The mean exposure duration to VX-445/TEZ/IVA was 23.6 weeks in Study 102, 4.0 weeks in Study 103 and 21.5 weeks in Study 105.

Over 700 unique subjects received at least 1 dose of VX-445 as monotherapy or as part of a TC regimen.

The Study 105 IA2 Safety Set included 506 subjects, who had a mean exposure duration of 37.2 weeks, representing 392.2 patient-years of exposure. The Cumulative Safety Set included 510 subjects who had a mean exposure duration of 46.7 weeks, representing 496.6 patient-years of exposure. A subset of 271 subjects received ≥48 weeks of VX-445/TEZ/IVA treatment and had a mean exposure of 57.2 weeks.

Table 28 Summary of Exposure: OL Safety Period and Cumulative Safety and Set of Subjects With Cumulative Exposure of ≥ 48 Weeks-

	Study 105 IA2 Safety Set	Cumulative Safety Set	Cumulative Safety Set Exposure ≥ 48 weeks
	Any VX-445/TEZ/IVA N = 506	Any VX-445/TEZ/IVA N = 510	Any VX-445/TEZ/IVA N = 271
Total exposure (patient-years)	392.2	496.6	322.7
Exposure duration (weeks)			
n	506	510	271
Mean (SD)	37.2 (8.92)	46.7 (13.31)	57.2 (6.09)
Median	36.5	49.0	55.1
Min, max	1.4, 55.4	1.0, 69.1	48.0, 69.1
Exposure duration by interval, n (%)			
≤24 weeks	13 (2.6	12 (2.4)	0
>24 to ≤48 weeks	443 (87.5)	229 (44.9)	0
>48 weeks to ≤72 weeks	50 (9.9)	269 (52.7)	271 (100.0)[a]

Sources: ISA2/Table 2.1.1.1, Table 2.1.1.2, and Ad Hoc Table 2.1.1.4
IA: interim analysis; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; OL: open label; TEZ: tezacaftor
[a] Number of subjects in the Cumulative Safety Period with exposure of ≥48 to ≤72 weeks.
Notes: Total exposure was defined as the sum total of the VX-445/TEZ/IVA exposure across all subjects in the applicable IA2 Safety Set (Study 105 or Cumulative). Duration of VX-445/TEZ/IVA exposure (weeks) = ([last dose date – first dose date] in the applicable Treatment-emergent Period + 1)/7, regardless of any interruptions in dosing. For subjects who were still on VX-445/TEZ/IVA at the IA2 data cutoff date, this date was used as the last dose date to calculate the duration of VX-445/TEZ/IVA exposure. Duration of
VX-445/TEZ/IVA exposure (years) = duration of VX-445/TEZ/IVA exposure (weeks)/48; 1 year = 48 weeks.

The safety profile of VX-445 in combination with TEZ/IVA was derived primarily from Study 102, a 24-week, placebo-controlled study in CF subjects, with the largest exposed population and the longest treatment duration. In addition, safety data from the second interim analysis (IA2) of the ongoing OLE Study 105 (as of the data cut-off date of 31 October 2019) has been submitted.

Adverse events

The safety profile of VX-445 in combination with TEZ/IVA was derived primarily from Study 102.

The overview of AEs in Study 102 Safety Set, and Study 105 Safety Set (OLE) is presented. The details are provided per safety set.

Study 102 Safety Set

The incidence of subjects with at least 1 AE was 93.1% in the VX-445/TEZ/IVA group and 96.0% in the placebo group. Twenty-eight (13.9%) subjects in the VX-445/TEZ/IVA group and 42 (20.9%) subjects in the placebo group had serious AEs (SAEs). The majority of subjects had AEs that were mild or moderate in severity. Nineteen (9.4%) subjects in the VX-445/TEZ/IVA group and 10 (5.0%) subjects in the placebo group interrupted study drug due to AEs. Two (1.0%) subjects in the VX-445/TEZ/IVA group and no subjects in the placebo group discontinued study drug due to AEs. There were no deaths, and no subjects in the VX-445/TEZ/IVA group had life-threatening AEs.

Study 103 Safety Set

The incidence of subjects with at least 1 AE was 58.2% in the VX-445/TEZ/IVA group and 63.5% in the TEZ/IVA group. Two (3.6%) subjects in the VX-445/TEZ/IVA group and 1 (1.9%) subject in the TEZ/IVA group had SAEs. The majority of subjects had AEs that were mild or moderate in severity. No subjects had AEs that led to study drug interruption or discontinuation. There were no deaths or life-threatening AEs.

Study 105

In the IA2, 471 (93.1%) subjects had at least 1 AE and 80 (15.8%) subjects had at least 1 serious adverse event (SAE). The majority AEs were mild or moderate in severity; 2 (0.4%) subjects had life-threatening AEs. Twenty-nine (5.7%) subjects interrupted VX-445/TEZ/IVA due to AEs, and 7 (1.4%) subjects discontinued VX-445/TEZ/IVA due to AEs. There were no deaths.

Table 29 Overview of AEs (Study 102 Safety Set and Study 105 Safety Set IA2)

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Number of AEs (Total)	1287	--	1098	--	2909	--
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any AEs	193 (96.0)	1287.96	188 (93.1)	1096.01	471 (93.1)	739.87
Subjects with AEs by strongest relationship						
Not related	83 (41.3)	--	53 (26.2)	--	175 (34.6)	--
Unlikely related	58 (28.9)	--	39 (19.3)	--	127 (25.1)	--
Possibly related	46 (22.9)	--	86 (42.6)	--	146 (28.9)	--
Related	6 (3.0)	--	10 (5.0)	--	23 (4.5)	--
Subjects with AEs by maximum severity						
Mild	53 (26.4)	--	67 (33.2)	--	180 (35.6)	--
Moderate	125 (62.2)	--	102 (50.5)	--	238 (47.0)	--
Severe	14 (7.0)	--	19 (9.4)	--	51 (10.1)	--
Life-threatening	1 (0.5)	--	0	--	2 (0.4)	--
Missing	0	--	0	--	0	--
Subjects with AEs leading to VX-445/TEZ/IVA discontinuation	0	0	2 (1.0)	2.99	7 (1.4)	3.31
Subjects with AEs leading to VX-445/TEZ/IVA interruption	10 (5.0)	14.01	19 (9.4)	25.95	29 (5.7)	13.73
Subjects with Grade 3/4 AEs[a]	15 (7.5)	23.02	19 (9.4)	27.95	53 (10.5)	19.84
Subjects with related AEs[b]	52 (25.9)	140.10	96 (47.5)	210.62	169 (33.4)	97.92
Subjects with serious AEs	42 (20.9)	67.05	28 (13.9)	36.93	80 (15.8)	27.47
Subjects with related serious AEs[b]	2 (1.0)	2.00	6 (3.0)	5.99	13 (2.6)	5.09
Subjects with AEs leading to death	0	0	0	0	0	0

Source: ISA2 Table 2.3.1.1.1
AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PY: patient-year; SAE: serious adverse event; TEZ: tezacaftor
Note: A subject with multiple events within a category was counted only once in that category.
[a] Grade 3 indicates events of severe intensity; Grade 4 indicates events that were life-threatening.
[b] Related AEs and SAEs included related, possibly related, and missing categories.

Cumulative Safety Set

In IA2, the Cumulative Safety Set included safety data from all 510 subjects. A total of 488 (95.7%) subjects had at least 1 AE. The majority of subjects had AEs that were mild or moderate in severity. Two (0.4%) subjects had life-threatening AEs. SAEs were reported in 93 (18.2%) subjects. Ten (2.0%) subjects discontinued VX-445/TEZ/IVA due to AEs.

Overall, results from the Cumulative Safety Set were consistent with the safety data presented individually for Studies 102 and 103, as well as for Study 105.

Safety in Subjects Who Received VX-445/TEZ/IVA for At Least 48 Weeks

In IA2, a total of 265 (97.8%) subjects had at least 1 AE. The exposure-adjusted event rates for the majority of AEs were similar or lower than in the Study 102 VX-445/TEZ/IVA group. The majority of subjects had AEs that were mild or moderate in severity (63 mild (23.2%), 161 moderate (59.4%), 41 severe (15.1%)). There were no life-threatening AEs.
A total of 50 (18.5%) subjects had at least 1 SAE. The exposure-adjusted rates for SAEs were similar or lower than in the Study 102 VX-445/TEZ/IVA group.

No subjects had AEs that led to treatment discontinuation; 26 (9.6%) subjects had AEs that led to treatment interruption.

Overview of AEs in Healthy Subjects

In the pooled analysis of Phase 1 Studies in Healthy Subjects, 43 (22.5%) subjects in the Any VX-445 group and 13 (24.1%) subjects in the placebo group had at least 1 AE. In both groups, the majority of AEs were mild in severity; there were no SAEs or deaths. One (1.9%) subject in the placebo group had a severe AE.

There were 2 (1.0%) subjects in the Any VX-445 group and 1 (1.9%) subject in the placebo group who had AEs that led to treatment discontinuation. There were no AEs that led to treatment interruption in any group.

Common AEs

The AEs with an incidence of ≥5% of Study 102 Safety Set, and Study 105 Safety Set (OLE) is presented in Table 31. The details are provided per safety set.

Study 102 Safety Set

Overall, the AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older.

AEs occurring in ≥8% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group were headache, diarrhoea, upper respiratory tract infection, abdominal pain, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, blood creatine phosphokinase increased, nasal congestion, rash, and rhinorrhoea; each occurred in ≤20% of subjects in the VX-445/TEZ/IVA group.

Among the AEs with an incidence of ≥5% in any group, AEs occurring in < 8% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group were, sinusitis, rhinitis, influenza, and blood bilirubin increased.

Blood bilirubin increased was observed with VX-445/TEZ/IVA treatment; this finding is consistent with the OATP1B1 and OATP1B3 transporter inhibition effect by VX-445.

The study was conducted through the winter season, and most of the AEs of influenza occurred during that time. In the VX-445/TEZ/IVA group, none of the AEs of influenza were considered related to study drug and all subjects continued study drug dosing, except 2 subjects who resumed treatment after an interruption.

Lastly, there was a lower rate of AEs reported in the infections and infestations SOC overall in the VX-445/TEZ/IVA group compared with the placebo group.

Study 103 Safety Set,

In the Study 103 Safety Set, Study 105 Safety Set and Cumulative Safety Set, among the AEs with an incidence of ≥5% in any group, the AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older. presents the AEs with an incidence of ≥5% in any group.

Table 30 AEs With an Incidence of At Least 5% in Any Group by PT: Study 103 Safety Set

	Treatment Period	
	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Preferred Term	n (%)	n (%)
Subjects with any AEs	33 (63.5)	32 (58.2)
Cough	4 (7.7)	8 (14.5)
Nasopharyngitis	2 (3.8)	4 (7.3)
Oropharyngeal pain	0	4 (7.3)
Upper respiratory tract infection	2 (3.8)	4 (7.3)
Abdominal pain	1 (1.9)	3 (5.5)
Fatigue	2 (3.8)	3 (5.5)
Headache	4 (7.7)	3 (5.5)
Nasal congestion	1 (1.9)	3 (5.5)
Respiration abnormal	0	3 (5.5)
Sputum increased	3 (5.8)	3 (5.5)
Diarrhoea	3 (5.8)	2 (3.6)
Haemoptysis	5 (9.6)	2 (3.6)
Infective PEx of CF	6 (11.5)	1 (1.8)
Nausea	3 (5.8)	1 (1.8)

Source: Study 103 CSR/Table 14.3.1.3
AE: adverse event; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor
Notes: MedDRA Version 21.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency of the VX-445/TEZ/IVA column by PT.

Study 105 Safety Set

The exposure-adjusted event rates for the majority of AEs were similar or lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group.

In IA2, 471 (93%) subjects experienced an AE. The AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older.

The exposure-adjusted event rates for the majority of AEs were similar or lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group. Table 31 presents the AEs with an incidence of ≥5%.

Table 31 AEs With an Incidence of At Least 5% by PT (Study 102 Safety Set and Study 105 Safety Set) Treatment-emergent AEs

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any AEs	193 (96.0)	1287.96	188 (93.1)	1096.01	471 (93.1)	739.87
Infective PEx of CF	95 (47.3)	181.13	44 (21.8)	64.88	127 (25.1)	49.60
Cough	77 (38.3)	113.08	34 (16.8)	38.93	118 (23.3)	44.26
Oropharyngeal pain	25 (12.4)	26.02	20 (9.9)	26.95	74 (14.6)	25.69
Nasopharyngitis	26 (12.9)	34.03	22 (10.9)	29.95	69 (13.6)	21.62
Headache	30 (14.9)	42.03	35 (17.3)	48.91	66 (13.0)	24.93
Sputum increased	39 (19.4)	47.03	40 (19.8)	46.91	63 (12.5)	20.60
Upper respiratory tract infection	22 (10.9)	26.02	24 (11.9)	29.95	60 (11.9)	18.31
Fatigue	20 (10.0)	22.02	9 (4.5)	8.98	51 (10.1)	16.28
Nasal congestion	15 (7.5)	18.01	19 (9.4)	20.96	48 (9.5)	16.79
Pyrexia	19 (9.5)	25.02	17 (8.4)	17.97	44 (8.7)	12.46
Diarrhoea	14 (7.0)	23.02	26 (12.9)	31.94	38 (7.5)	10.43
Haemoptysis	28 (13.9)	42.03	11 (5.4)	11.98	36 (7.1)	15.77
Rash	9 (4.5)	12.01	19 (9.4)	24.95	35 (6.9)	11.19
Nausea	14 (7.0)	17.01	16 (7.9)	15.97	32 (6.3)	8.65
Blood creatine phosphokinase increased	9 (4.5)	9.01	19 (9.4)	19.96	31 (6.1)	8.90
Sinusitis	8 (4.0)	8.01	11 (5.4)	14.97	31 (6.1)	10.17
Sinus congestion	8 (4.0)	10.01	7 (3.5)	7.99	29 (5.7)	8.90
Abdominal pain	12 (6.0)	20.01	20 (9.9)	23.96	27 (5.3)	7.63
ALT increased	7 (3.5)	8.01	20 (9.9)	21.96	27 (5.3)	7.88
AST increased	4 (2.0)	4.00	19 (9.4)	20.96	27 (5.3)	7.88
Rhinitis	11 (5.5)	14.01	15 (7.4)	17.97	27 (5.3)	8.39
Vomiting	10 (5.0)	13.01	12 (5.9)	13.97	27 (5.3)	8.39

Source: ISA2 Table 2.3.1.3

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; PT: Preferred Term; PY: patient-year; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

Cumulative Safety Set

The AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older. Overall, results from the Cumulative Safety Set were consistent with the safety data from parent Studies 102 and 103, as well as for Study 105.

Subjects who received VX-445/TEZ/IVA for at least 48 weeks

In the set of subjects who received VX-445/TEZ/IVA for at least 48 weeks, 57 (98.3%) subjects had at least 1 AE. In IA2, a total of 265 (97.8%) subjects had at least 1 AE. The AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older or with the safety profile for VX-445/TEZ/IVA of study 102 and study 105.

AEs that occurred in ≥5% of subjects who received VX-445/TEZ/IVA for at least 48 weeks cumulatively across studies (as of Study 105 IA2) are summarized in Table 32.

Table 32 AEs With an Incidence of At Least 5% by PT: Subjects With Cumulative TC Exposure of At Least 48 Weeks

Preferred Term	Any VX-445/TEZ/IVA N = 271 n (%)
Subjects with any AEs	256 (94.5)
Infective PEx of CF	97 (35.8)
Cough	87 (32.1)
Sputum increased	69 (25.5)
Oropharyngeal pain	68 (25.1)
Headache	60 (22.1)
Upper respiratory tract infection	59 (21.8)
Nasopharyngitis	52 (19.2)
Nasal congestion	48 (17.7)
Diarrhoea	43 (15.9)
Fatigue	40 (14.8)
Blood creatine phosphokinase increased	39 (14.4)
Pyrexia	39 (14.4)
Abdominal pain	34 (12.5)
ALT increased	33 (12.2)
Rash	33 (12.2)
Sinusitis	32 (11.8)
Rhinorrhoea	30 (11.1)
AST increased	29 (10.7)
Haemoptysis	29 (10.7)
Nausea	28 (10.3)
Vomiting	27 (10.0)
Rhinitis	26 (9.6)
Influenza	25 (9.2)
Productive cough	22 (8.1)
Respiration abnormal	22 (8.1)
Sinus congestion	22 (8.1)
Abdominal pain upper	18 (6.6)
Constipation	17 (6.3)
Dyspnoea	17 (6.3)
Hypoglycaemia	16 (5.9)
Seasonal allergy	16 (5.9)
Viral upper respiratory tract infection	16 (5.9)
Acne	15 (5.5)
Arthralgia	15 (5.5)
Blood bilirubin increased	14 (5.2)
Lower respiratory tract congestion	14 (5.2)

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

AEs by Relationship

Study 102 Safety Set

Ten (5.0%) subjects in the VX-445/TEZ/IVA group and 6 (3.0%) subjects in the placebo group had an AE assessed by the investigator as related; 86 (42.6%) subjects in the VX-445/TEZ/IVA group and 46 (22.9%) subjects in the placebo group had an AE assessed by the investigator as possibly related.

Related (combined related or possibly related) AEs occurring in≥5 subjects in any treatment group are presented in Table 33.

Table 33 Related AEs Occurring in ⩾5 Subjects in Any Treatment Group (Safety Set)

System Organ Class Preferred Term	Placebo N = 201 n (%)	VX-445/TEZ/IVA N = 202 n (%)
Subjects with any related AEs	52 (25.9)	96 (47.5)
Respiratory, thoracic and mediastinal disorders	25 (12.4)	29 (14.4)
Sputum increased	10 (5.0)	14 (6.9)
Cough	13 (6.5)	7 (3.5)
Productive cough	5 (2.5)	7 (3.5)
Investigations	9 (4.5)	26 (12.9)
ALT increased	1 (0.5)	12 (5.9)
AST increased	0	11 (5.4)
Blood CK increased	2 (1.0)	10 (5.0)
Blood bilirubin increased	0	6 (3.0)
Gastrointestinal disorders	12 (6.0)	22 (10.9)
Abdominal pain upper	3 (1.5)	5 (2.5)
Skin and subcutaneous tissue disorders	7 (3.5)	18 (8.9)
Rash	3 (1.5)	11 (5.4)
Nervous system disorders	10 (5.0)	11 (5.4)
Headache	8 (4.0)	9 (4.5)

Source: Table 14.3.1.6

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine phosphokinase; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class; TEZ: tezacaftor

Note: AEs were coded using MedDRA version 22.0. A subject with multiple events within a category was counted only once in that category. Table was sorted in descending order of frequency of the

Study 103 Safety Set

Twelve (21.8%) subjects in the VX-445/TEZ/IVA group and 9 (17.3%) subjects in the TEZ/IVA group had at least 1 event considered related or possibly related to study drug**.** One (1.8%) subject in the VX-445/TEZ/IVA group and 1 (1.9%) subject in the TEZ/IVA group had an AE assessed by the investigator as related. Eleven (20.0%) subjects in the VX-445/TEZ/IVA group and 8 (15.4%) subjects in the TEZ/IVA group had an AE assessed by the investigator as possibly related.

The most frequent related in order of highest frequency is respiration abnormal (5.5%) while all other events were only observed in 1 or 2 patients.

In TEZ/IVA group following possibly related or related events were observed: AST increased, cough, Sputum increased, haemoptysis, rhinorrhoea, infective PEx, abdominal pain, diarrhoea, nausea, Rectal haemorrhage, fatigue, headache, rash (2).
In VX-445/TEZ/IVA group cough (2), respiration abnormal (3), oropharyngeal pain (2), sputum increase (2), haemoptysis, increased bronchial secretion, rhinorrhoea, sputum discoloured, Sputum retention, wheezing, abdominal pain, fatigue, chest discomfort, headache (2), aphonia, lethargy, trigeminal neuralgia, rash, hyperhidrosis, ALT increased, AST increased, blood alkaline phosphatase increased, transaminases increased, muscle spasms, vaginal discharge were found as possibly related or related events.

No clear conclusion can be drawn for this data set.

Study 105 Safety Set

In IA2, 169 (33.4%) subjects had AEs considered related or possibly related to VX-445/TEZ/IVA.

Related AEs that occurred in ≥5 subjects in Study 105 IA2 are summarized in Table 34. The most common related AEs were generally consistent with common manifestations and complications of CF disease or with the established safety profile for VX-445/TEZ/IVA. Related AEs of photosensitivity reaction occurred in 7 subjects.

Table 34 Related AEs Occurring in At Least 5 Subjects by PT: OL (Study 105) Safety Set

Preferred Term	Any VX-445/TEZ/IVA N = 506 n (%)
Subjects with any related AEs	129 (25.5)
ALT increased	23 (4.5)
AST increased	22 (4.3)
Blood creatine phosphokinase increased	19 (3.8)
Cough	18 (3.6)
Sputum increased	16 (3.2)
Blood bilirubin increased	14 (2.8)
Rash	12 (2.4)
Diarrhoea	9 (1.8)
Headache	8 (1.6)
Gamma-glutamyltransferase increased	8 (1.6)
Photosensitivity reaction	7 (1.4)
Abdominal pain	6 (1.2)
Hypoglycaemia	6 (1.2)
Respiration abnormal	5 (1.0)
Fatigue	5 (1.0)
Infective PEx of CF	5 (1.0)

Source: Study 105 IA2 Ad Hoc Table 2.3.1.9

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted. The table was sorted in descending order of frequency by PT.

Cumulative Safety Set and Subjects who received VX-445/TEZ/IVA for at least 48 weeks

In both the overall cumulative analysis and the 48-week cumulative exposure analysis, the most common related AEs were generally consistent with common manifestations and complications of CF disease or with the established safety profile for VX-445/TEZ/IVA. In addition, exposure-adjusted analyses of event rates in Study 102 compared with Study 105 showed a decrease in the rates of the majority of related AEs with longer-term treatment.

Related AEs that occurred in ≥5 subjects who received VX-445/TEZ/IVA for at least 48 weeks cumulatively across studies (as of Study 105 IA2) are summarized in Table 35.

Table 35 Related AEs Occurring in At Least 5 Subjects by PT: Cumulative TC Safety Period (Cumulative TC Safety Set, Subjects With Cumulative TC Exposure of At Least 48 Weeks)

Preferred Term	Any VX-445/TEZ/IVA N = 271 n (%)
Subjects with any related AEs	114 (42.1)
ALT increased	23 (8.5)
Sputum increased	22 (8.1)
Blood creatine phosphokinase increased	21 (7.7)
AST increased	19 (7.0)
Cough	14 (5.2)
Rash	14 (5.2)
Headache	12 (4.4)
Respiration abnormal	10 (3.7)
Blood bilirubin increased	9 (3.3)
Haemoptysis	8 (3.0)
Diarrhoea	7 (2.6)
Fatigue	7 (2.6)
Productive cough	7 (2.6)
Abdominal pain	6 (2.2)
Hypoglycaemia	6 (2.2)
Pruritus	6 (2.2)
Rhinorrhoea	6 (2.2)
Abdominal pain upper	5 (1.8)
Blood alkaline phosphatase increased	5 (1.8)
Nausea	5 (1.8)

Source: ISA2 Ad Hoc Table 2.3.1.10

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted. The table was sorted in descending order of frequency by PT.

AEs by severity

The grade 3/4 AEs with an incidence of ≥5% of Study 102 Safety Set, and Study 105 IA2 Safety Set (OLE) and Cumulative Safety Set are presented in Table 36. The details are provided per safety set.

Study 102 Safety Set

The majority of subjects overall had AEs that were mild (29.8%) or moderate (56.3%) in severity.

In the VX-445/TEZ/IVA group, 19 (9.4%) subjects had severe AEs and no subjects had life-threatening AEs. In the placebo group, 14 (7.0%) subjects had severe AEs and 1 (0.5%) subject had a life-threatening AE of neuroglycopenia.

Study 105 Safety Set

In IA2, 51 (10.1%) subjects had severe (Grade 3) AEs and 2 (0.4%) subjects had life-threatening (Grade 4) AEs. The exposure-adjusted event rate for Grade 3/4 AEs was lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group (19.84 versus 27.95 events/100PY).

Brief descriptions of the 2 subjects who had life-threatening AEs are provided below.

- One subject with a medical history of depression had a life-threatening AE of suicide attempt, which was considered by the investigator to be not related to VX-445/TEZ/IVA. The event resolved without change to VX-445/TEZ/IVA dosing.

- One subject with a medical history of recurrent haemoptysis had a life-threatening AE of pulmonary haemorrhage, which was considered to be possibly related to VX-445/TEZ/IVA. The event resolved with interruption of VX-445/TEZ/IVA, which has since been resumed.

Table 36 Grade 3/4 TEAEs by System Organ Class and Preferred Term - Study 102 Safety Period, OL Safety Period

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
System Organ Class Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any Grade 3/4 TEAEs	15 (7.5)	23.02	19 (9.4)	27.95	53 (10.5)	19.84
Infections and infestations	9 (4.5)	12.01	3 (1.5)	3.99	23 (4.5)	6.87
Infective pulmonary exacerbation of cystic fibrosis	9 (4.5)	11.01	0	0	16 (3.2)	4.58
Influenza	0	0	0	0	3 (0.6)	1.02
Bronchopulmonary aspergillosis allergic	0	0	0	0	1 (0.2)	0.25
Chronic sinusitis	0	0	0	0	1 (0.2)	0.25
Genital herpes simplex	0	0	1 (0.5)	1.00	0	0
Infective exacerbation of bronchiectasis	1 (0.5)	1.00	0	0	1 (0.2)	0.25
Oral herpes	0	0	1 (0.5)	1.00	0	0
Pneumonia	0	0	1 (0.5)	1.00	1 (0.2)	0.25
Urinary tract infection	0	0	1 (0.5)	1.00	0	0
Vascular device infection	0	0	0	0	1 (0.2)	0.25
Investigations	0	0	6 (3.0)	8.98	10 (2.0)	4.83
Blood creatine phosphokinase increased	0	0	4 (2.0)	3.99	4 (0.8)	1.02
Aspartate aminotransferase increased	0	0	2 (1.0)	2.00	4 (0.8)	1.27
Alanine aminotransferase increased	0	0	2 (1.0)	2.00	3 (0.6)	1.02
Gamma-glutamyltransferase increased	0	0	1 (0.5)	1.00	2 (0.4)	0.76
Blood bilirubin increased	0	0	0	0	1 (0.2)	0.25
Blood immunoglobulin E increased	0	0	0	0	1 (0.2)	0.25
Influenza A virus test positive	0	0	0	0	1 (0.2)	0.25
Gastrointestinal disorders	2 (1.0)	4.00	4 (2.0)	3.99	7 (1.4)	2.29
Distal intestinal obstruction syndrome	0	0	1 (0.5)	1.00	4 (0.8)	1.27
Gastritis	0	0	0	0	2 (0.4)	0.51
Abdominal pain	0	0	1 (0.5)	1.00	0	0
Abdominal pain upper	0	0	1 (0.5)	1.00	0	0
Gastric haemorrhage	0	0	0	0	1 (0.2)	0.25
Small intestinal obstruction	1 (0.5)	2.00	1 (0.5)	1.00	0	0

Toothache	0	0	0	0	1 (0.2)	0.25
Nausea	1 (0.5)	1.00	0	0	0	0
Vomiting	1 (0.5)	1.00	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.5)	1.00	3 (1.5)	2.99	4 (0.8)	1.27
Haemoptysis	1 (0.5)	1.00	1 (0.5)	1.00	1 (0.2)	0.25
Lung infiltration	0	0	0	0	1 (0.2)	0.25
Nasal polyps	0	0	1 (0.5)	1.00	0	0
Painful respiration	0	0	0	0	1 (0.2)	0.25
Productive cough	0	0	1 (0.5)	1.00	0	0
Pulmonary haemorrhage	0	0	0	0	1 (0.2)	0.51
Hepatobiliary disorders	1 (0.5)	1.00	2 (1.0)	2.00	2 (0.4)	0.51
Cholangitis	0	0	1 (0.5)	1.00	0	0
Cholecystitis acute	0	0	0	0	1 (0.2)	0.25
Gallbladder enlargement	0	0	1 (0.5)	1.00	0	0
Hepatic steatosis	0	0	0	0	1 (0.2)	0.25
Hepatocellular injury	1 (0.5)	1.00	0	0	0	0
Psychiatric disorders	0	0	0	0	3 (0.6)	0.76
Suicide attempt	0	0	0	0	2 (0.4)	0.51
Psychotic disorder	0	0	0	0	1 (0.2)	0.25
Cardiac disorders	0	0	0	0	2 (0.4)	0.51
Arrhythmia	0	0	0	0	1 (0.2)	0.25
Pericardial effusion	0	0	0	0	1 (0.2)	0.25
General disorders and administration site conditions	0	0	2 (1.0)	2.00	0	0
Adverse drug reaction	0	0	1 (0.5)	1.00	0	0
Pyrexia	0	0	1 (0.5)	1.00	0	0
Injury, poisoning and procedural complications	0	0	1 (0.5)	1.00	1 (0.2)	0.25
Post procedural haemorrhage	0	0	1 (0.5)	1.00	0	0
Procedural pain	0	0	0	0	1 (0.2)	0.25
Musculoskeletal and connective tissue disorders	1 (0.5)	1.00	1 (0.5)	1.00	1 (0.2)	0.25
Joint stiffness	0	0	0	0	1 (0.2)	0.25
Rhabdomyolysis	0	0	1 (0.5)	1.00	0	0
Back pain	1 (0.5)	1.00	0	0	0	0
Nervous system disorders	2 (1.0)	2.00	0	0	2 (0.4)	0.51
Headache	0	0	0	0	1 (0.2)	0.25
Hepatic encephalopathy	0	0	0	0	1 (0.2)	0.25
Migraine	1 (0.5)	1.00	0	0	0	0
Neuroglycopenia	1 (0.5)	1.00	0	0	0	0
Renal and urinary disorders	0	0	0	0	2 (0.4)	0.51
Calculus urinary	0	0	0	0	1 (0.2)	0.25
Nephrolithiasis	0	0	0	0	1 (0.2)	0.25
Reproductive system and breast disorders	0	0	0	0	2 (0.4)	0.51
Ovarian cyst	0	0	0	0	1 (0.2)	0.25
Vaginal haemorrhage	0	0	0	0	1 (0.2)	0.25
Skin and subcutaneous tissue disorders	1 (0.5)	1.00	1 (0.5)	2.00	1 (0.2)	0.25
Rash	0	0	1 (0.5)	1.00	1 (0.2)	0.25
Pruritus	0	0	1 (0.5)	1.00	0	0
Hypersensitivity vasculitis	1 (0.5)	1.00	0	0	0	0
Metabolism and nutrition disorders	1 (0.5)	1.00	0	0	1 (0.2)	0.51
Hypoglycaemia	1 (0.5)	1.00	0	0	1 (0.2)	0.51

- MedDRA version 22.1.
- Events/100PY: number of events per 100 patient years (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100PY.
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- A subject with missing severity levels is not counted.
- Table is sorted in descending order of frequency of the Any VX-445/TEZ/IVA column during the Cumulative TC Safety Period by System Organ Class, and by Preferred Term within each System Organ Class.

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Study 103 Safety Set

The majority of AEs in both the VX-445/TEZ/IVA and TEZ/IVA groups were mild (41.1%) or moderate (18.7%) in severity. No subject in the VX-445/TEZ/IVA group and 1 (1.9%) subject in the TEZ/IVA group had a severe AE (musculoskeletal pain). There were no life-threatening AEs.

Cumulative Safety Set

Two (0.4%) subjects had life-threatening AEs (as in Study 105).

Subjects who received VX-445/TEZ/IVA for at least 48 weeks

The majority of subjects had AEs that were mild or moderate in severity (63 mild (23.2%), 161 moderate (59.4%).

A total of 41 (15.1%) subjects had at least 1 AE that was Grade 3 or 4 in severity. Grade 3/4 events that occurred in ≥2 subjects were infective PEx of CF (10 subjects), blood creatine phosphokinase increased (8 subjects), DIOS (4 subjects), AST increased (4 subjects), ALT increased (3 subjects), GGT increased (2 subjects), gastritis (2 subjects), and influenza (2 subjects).

There were no life-threatening AEs.

The majority of events were assessed by the investigator as unrelated (not related or unlikely related) to VX-445/TEZ/IVA treatment and generally resolved without changes to study drug dosing.

The overall exposure-adjusted rate for Grade 3/4 AEs was similar between the population who received VX-445/TEZ/IVA for at least 48 weeks as of Study 105 IA2 and the placebo group in Study 102 (21.07 and 23.02 events per 100PY, respectively.

Serious adverse event/deaths/other significant events

Deaths

There were no AEs leading to death during the clinical program.

Serious adverse events

The SAEs of at least 2 subjects in Study 102 Safety Set, and Study 105 IA2 Safety Set (OLE) are presented in Table 36. The details are provided per safety set.

Study 102 Safety Set

Twenty-eight (13.9%) subjects in the VX-445/TEZ/IVA group and 42 (20.9%) subjects in the placebo group had at least 1 SAE.

Overall, the SAEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older.

SAEs that occurred in ≥2 subjects in any group and were more common in the VX-445/TEZ/IVA group than the placebo group included rash and influenza. Rash events are further discussed below. The 3 SAEs of influenza in the VX-445/TEZ/IVA group were all assessed by the investigator as not related to study drug.

The majority of SAEs were assessed by the investigator as unlikely related or not related to study drug.

Study 105

In IA2, a total of 80 (15.8%) subjects had SAEs. Overall, the SAEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older.

The exposure-adjusted event rate for SAEs was lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group (27.47 versus 36.93 events/100PY).

SAEs that occurred in ≥2 subjects are summarized in Table 37.

Table 37 Serious AEs Occurring in At Least 2 Subjects by PT: Study 105 Safety Set

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100PY	--	1.00	--	1.00	--	3.93
Infective PEx of CF	33 (16.4)	44.03	11 (5.4)	11.98	42 (8.3)	12.21
Distal intestinal obstruction syndrome	0	0	1 (0.5)	1.00	5 (1.0)	1.53
Hemoptysis	3 (1.5)	3.00	2 (1.0)	2.00	5 (1.0)	1.53
Vascular device infection	0	0	0	0	3 (0.6)	0.76
Influenza	0	0	3 (1.5)	2.99	2 (0.4)	0.51
ALT increased	0	0	0	0	2 (0.4)	0.51
AST increased	0	0	0	0	2 (0.4)	0.51

Source: ISA2 Table 2.3.2.4.1

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; PT: Preferred Term; PY: patient-year; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

Study 103 Safety Set

In the VX-445/TEZ/IVA group, 2 (3.6%) subjects had SAEs: 1 subject had an SAE of infective pulmonary exacerbation (PEx) of CF and 1 subject had an SAE of rash. In the TEZ/IVA group, 1 (1.9%) subject had an SAE of infective PEx of CF.

Cumulative Safety Set

SAEs were reported in 72 (14.1%) subjects. SAEs that occurred in > 2 subjects were infective PEx of CF, distal intestinal obstruction syndrome, haemoptysis, influenza, and rash. In IA2, additionally vascular device infection, ALT increased, and AST increased occurred. All other SAEs occurred in a single subject each.

Safety in subjects who received VX-445/TEZ/IVA for at least 48 weeks

In IA2, 50 (18.5%) subjects had at least 1 SAE. SAEs that occurred in ≥2 subjects were infective PEx of CF, influenza, DIOS, haemoptysis, rash, and vascular device infection;

Related serious adverse events

Study 102 Safety Set, Study 105 IA2 Safety Set, Cumulative Safety Set

Cumulatively across the parent Studies 102 and 103 and Study 105 IA2, 20 (3.9%) subjects who received any VX-445/TEZ/IVA had related SAEs: 6 subjects with related SAEs in Study 102, and 1 subject with a related SAE in Study 103 and 13 subjects with related SAEs in Study 105.
Related SAEs that occurred in ≥2 subjects in the Cumulative TC Safety Period were haemoptysis, rash, distal intestinal obstruction syndrome (DIOS), infective PEx of CF, alanine transaminase (ALT)

increased, and aspartate transaminase (AST) increased; all other related SAEs occurred in 1 subject each.

Overall, the incidence of related SAEs was low across studies. The majority of these events were consistent with common manifestations and complications of CF disease or with the established safety profile for VX-445/TEZ/IVA. Many of these events had plausible alternative aetiologies and/or confounding factors (e.g., pre-existing medical history, concurrent infections or illnesses), and most of the subjects were able to maintain or successfully resume study drug dosing.
The findings of Study 102 Safety Set, Study 105 IA2 Safety Set, Cumulative Safety Set are presented in Table 38.

Table 38 Related Serious TEAEs by System Organ Class and Preferred Term - Study 102 Safety Period, OL Safety Period IA2, and Cumulative TC Safety Period Study 102 Safety Set, OL Safety Set, and Cumulative TC Safety Set

	Study 102		Study 105 (OLS)	Cumulative TC Safety Period
Preferred Term, n (%)	Placebo in 445-102 N = 201	VX-445/TEZ/IVA in 445-102 N = 202	Any VX-445/TEZ/IVA N = 506	Any VX-445/TEZ/IVA N = 510
Subjects with any related SAEs	2 (1.0)	6 (3.0)	13 (2.6)	20 (3.9)
Haemoptysis	0	1 (0.5)	2 (0.4)	3 (0.6)
Rash	0	1 (0.5)	1 (0.2)	3 (0.6)[a]
Distal intestinal obstruction syndrome	0	0	2 (0.4)	2 (0.4)
Infective PEx of CF	0	0	2 (0.4)	2 (0.4)
ALT increased	0	0	2 (0.4)	2 (0.4)
AST increased	0	0	2 (0.4)	2 (0.4)
Abdominal pain upper	0	1 (0.5)	0	1 (0.2)
Duodenitis	0	0	1 (0.2)	1 (0.2)
Pulmonary haemorrhage	0	0	1 (0.2)	1 (0.2)
Rash pruritic	0	1 (0.5)	0	1 (0.2)
Blood bilirubin increased	0	0	1 (0.2)	1 (0.2)
Gamma-glutamyltransferase increased	0	0	1 (0.2)	1 (0.2)
Arrhythmia	0	0	1 (0.2)	1 (0.2)
Portal hypertension	0	1 (0.5)	0	1 (0.2)
Rhabdomyolysis	0	1 (0.5)	0	1 (0.2)
Hepatic encephalopathy	0	0	1 (0.2)	1 (0.2)
Psychotic disorder	0	0	1 (0.2)	1 (0.2)
Painful respiration	1 (0.5)	0	0	0
Hypersensitivity vasculitis	1 (0.5)	0	0	0

Source: ISA2 Table 2.3.2.5
AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; OLS: open-label study; PEx: pulmonary exacerbation; PT: Preferred Term; SAE: serious adverse event; TC: triple combination; TEZ: tezacaftor
Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related SAEs, SAEs with relationship of related, possibly related, and missing were counted. The table was sorted in descending order of frequency of the Any VX-445/TEZ/IVA column during the Cumulative TC Safety Period by PT.
[a] One related SAE of rash occurred in Study 103.

No results of related serious events was provided for subjects who received VX-445/TEZ/IVA for at least 48 weeks.

Study 103 Safety Set

The SAE of rash in VX-445/TEZ/IVA was assessed by the investigator as related.

Events of specific interest

Prespecified events of special interest are transaminase elevation events and rash events. Data relevant to the assessment of blood bilirubin and creatine kinase are also discussed.

Transaminase Elevations

Liver function test (LFT) elevations have been seen in CF patients, including some receiving IVA monotherapy, TEZ/IVA, and VX-445/TEZ/IVA. Therefore, a comprehensive analysis of liver-related data in VX-445 clinical studies was performed.

The Liver function test (LFT) elevations in Study 102 Safety Set, and Study 105 IA2 Safety Set (OLE) are presented in Table 39. The details are provided per safety set.

Study 102 Safety Set

Twenty-two (10.9%) subjects in the VX-445/TEZ/IVA group and 8 (4.0%) subjects in the placebo group had at least 1 elevated transaminase event. The majority of events were mild or moderate in severity and were associated with ALT/AST elevations <5 × the upper limit of normal (ULN).

There were no elevated transaminase events that led to treatment discontinuation. Two (1.0%) subjects in the VX-445/TEZ/IVA group and 3 (1.5%) subjects in the placebo group had elevated transaminase events that led to treatment interruption: 1 of the subjects in the VX-445/TEZ/IVA group resumed treatment; the other subject enrolled in the open-label extension study while still on study drug interruption and eventually discontinued from the open-label extension study without resuming study drug.

No subjects in the VX-445/TEZ/IVA group and 1 subject (0.5%) in the placebo group had a serious elevated transaminase event.

The median time to onset of first elevated transaminase event was 57.0 days (range: 1, 176) in the VX-445/TEZ/IVA group and 58.0 days (range: 1, 169) in the placebo group. The median duration of elevated transaminase events was 17.0 days (range: 4,153) in the VX-445/TEZ/IVA group and 17.0 days (range: 5, 52) in the placebo group.

Additional relevant hepatic AEs occurred in 3 (1.5%) subjects in the VX-445/TEZ/IVA group (hepatic cirrhosis, hepatocellular injury, and portal hypertension) and 1 (0.5%) subject in the placebo group (hepatocellular injury). Events in the VX-445/TEZ/IVA group were as follows:

- The event of portal hypertension was an SAE in a subject with a medical history of hepatic cirrhosis that led to discontinuation of VX-445/TEZ/IVA treatment; it was assessed by the investigator as being of moderate severity and possibly related to study drug.
- The event of hepatocellular injury was a non-serious AE that was associated with mildly elevated transaminases (<2 × ULN) and was assessed by the investigator as being of mild severity and related to study drug. There was no change to study drug dosing.
- The event of hepatic cirrhosis was a non-serious AE that was associated with mildly elevated transaminases (<2 × ULN) and was assessed by the investigator as being of mild severity and unlikely related to study drug. There was no change to study drug dosing.
- The AE of hepatocellular injury in the placebo group was associated with transaminase elevations >8 × ULN and resulted in study drug interruption.

Mean concentrations of transaminase parameters were variable over time in both groups. In the VX-445/TEZ/IVA group, increases from baseline in mean ALT and AST were observed. The mean (SD) increases in ALT ranged from 4.8 (20.5) U/L at Week 16 to 8.2 (28.9) U/L at Week 24. The mean (SD)

increases in AST ranged from 3.2 (13.5) U/L at Week 16 to 6.6 (31.6) U/L at Week 24. In the placebo group, there were no trends in ALT or AST.

An overview of subjects with ALT and/or AST elevations by predefined thresholds and of subjects with ALT and/or AST elevations >3 × ULN and total bilirubin elevation >2 × ULN is presented in Table 39. The ALT/AST and bilirubin elevations did not have to be concurrent and could occur at any time in the Treatment-emergent Period, regardless of baseline levels.

The majority of subjects had ALT and AST values that remained within the normal range. More subjects in the VX-445/TEZ/IVA group had ALT or AST >3×, 5× and 8× ULN, respectively, compared to subjects in the placebo group. No subject had elevations of ALT or AST >3 × ULN concurrent with a newly occurring elevation in total bilirubin >2 × ULN. Two subjects in the VX-445/TEZ/IVA group had ALT or AST >3 × ULN and total bilirubin >2 × ULN during the study; in 1 subject, the elevations were not concurrent (ALT and AST >3 × ULN occurred at the Day 15 Visit; total bilirubin >2 × ULN occurred at the Week 24 Visit). The other subject had a medical history of Gilbert's syndrome and an elevated total bilirubin at screening >2 × ULN that remained high throughout the study.

Table 39 Threshold Analysis of Transaminase Elevations During the Treatment-emergent Period: Study 102 Safety Set

Parameter Post-baseline Threshold Analysis Criteria	Placebo N = 201 n/N1 (%)	VX-445/TEZ/IVA N = 202 n/N1 (%)
ALT or AST (U/L), interval		
>3 × to ≤5 × ULN	8 (4.0)	11 (5.4)
>5 × to ≤8 × ULN	1 (0.5)	2 (1.0)
ALT or AST (U/L), cumulative		
>3 × ULN	11 (5.5)	16 (7.9)
>5 × ULN	3 (1.5)	5 (2.5)
>8 × ULN	2 (1.0)	3 (1.5)
ALT or AST (U/L) and total bilirubin (µmol/L)		
ALT or AST >3 × ULN and total bilirubin >2 × ULN	0	2 (1.0)[a]

Source: Study 102 CSR/Table 14.3.4.2
ALT: alanine aminotransferase; AST: aspartate aminotransferase; IVA: ivacaftor; LFT: liver function test; n: size of subsample; N: total sample size; TEZ: tezacaftor; ULN: upper limit of normal
Notes: N1 was the number of subjects with at least 1 non-missing measurement during the Treatment-emergent Period and was equal to N for all categories in this table; n was the number of subjects in the post-baseline category. Within each parameter, a subject was counted in all applicable post-baseline categories based on the worst assessment during the Treatment-emergent Period. Percentages were evaluated as n/N1. Threshold criteria involving 2 LFT parameters could be determined by assessments at different visits during the Treatment-emergent Period.
[a] In 1 subject, the transaminase and bilirubin elevations were not concurrent. The other subject had a medical history of Gilbert's syndrome and an elevated total bilirubin at screening >2 × ULN, which remained high throughout the study.

Study 103 Safety Set

Two (3.6%) subjects in the VX-445/TEZ/IVA group and 1 (1.9%) subject in the TEZ/IVA group had at least 1 elevated transaminase event. All events were mild in severity, and none were serious or led to treatment discontinuation or interruption.

Increases from baseline in mean (SD) ALT and AST were observed in the VX-445/TEZ/IVA group (9.0 (16.5) U/L for ALT and 1.6 (13.9) U/L for AST), but not in the TEZ/IVA group (-3.1 (13.1) U/L for ALT and -2.0 (8.4) for AST).

The incidences of maximum transaminase elevations (ALT or AST) >3 ×, >5 ×, or >8 × ULN in the VX-445/TEZ/IVA group were 7.3%, 3.6%, and 0%, respectively. No subjects in the TEZ/IVA group had ALT or AST elevations >3 × ULN or ALT or AST >3 × ULN with total bilirubin >2 × ULN.

Study 105 Safety Set

In IA2, the incidences of subjects with maximum on-treatment transaminase elevations (ALT and/or AST) above thresholds of >3 ×, >5 ×, and >8 × ULN were 6.3%, 2.2.% and 0.6%, respectively. One subject had ALT or AST >3 × ULN and total bilirubin >2 × ULN during the study (not concurrent).

One additional subject had AST and ALT >3 × ULN concurrent with bilirubin >2 × ULN due to an SAE of acute cholecystitis, that were not captured in the clinical database nor included in the Study 105 IA tables and listings. This subject recovered quickly following a laparoscopic cholecystectomy, and ALT, AST, and bilirubin parameters returned to the subject's baseline levels (<2 × ULN).

Overall, the data related to transaminase elevations in Study 105 were consistent with those in the parent studies. (Table 40)

Table 40 Summary of AESI: Treatment-emergent Elevated Transaminase Events - Study 102 Safety Period, OL Safety Period

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any events	8 (4.0)	13.01	22 (10.9)	42.92	36 (7.1)	16.53
AST/ALT ratio abnormal	0	0	0	0	0	0
Alanine aminotransferase abnormal	0	0	0	0	0	0
Alanine aminotransferase increased	7 (3.5)	8.01	20 (9.9)	21.96	27 (5.3)	7.88
Aspartate aminotransferase abnormal	0	0	0	0	0	0
Aspartate aminotransferase increased	4 (2.0)	4.00	19 (9.4)	20.96	27 (5.3)	7.88
Hepatic enzyme abnormal	0	0	0	0	0	0
Hepatic enzyme increased	0	0	0	0	0	0
Hypertransaminasaemia	1 (0.5)	1.00	0	0	0	0
Liver function test abnormal	0	0	0	0	0	0
Liver function test increased	0	0	0	0	1 (0.2)	0.51
Transaminases abnormal	0	0	0	0	0	0
Transaminases increased	0	0	0	0	1 (0.2)	0.25
Subjects with any events by maximum severity						
Mild	4 (2.0)	--	12 (5.9)	--	20 (4.0)	--
Moderate	4 (2.0)	--	8 (4.0)	--	12 (2.4)	--
Severe	0	--	2 (1.0)	--	4 (0.8)	--
Life-threatening	0	--	0	--	0	--
Missing	0	--	0	--	0	--
Subjects with events leading to treatment discontinuation	0	0	0	0	3 (0.6)	1.53
Subjects with events leading to treatment interruption	3 (1.5)	4.00	2 (1.0)	2.99	11 (2.2)	5.09
Subjects with serious events	1 (0.5)	1.00	0	0	2 (0.4)	1.02
Subjects with related serious events	0	0	0	0	2 (0.4)	1.02
Subjects with events leading to death	0	0	0	0	0	0
Duration of events (days)						
Number of events	13	--	43	--	65	--
Number of events with non-missing duration	9	--	28	--	38	--
Mean (SD)	19.6 (14.6)	--	32.8 (34.0)	--	26.0 (16.9)	--
Median	17.0	--	17.0	--	24.0	--
Min, max	5, 52	--	4, 153	--	4, 57	--
Time-to-onset of first event (days)						
Subjects with event with complete start date	8	--	22	--	36	--
Mean (SD)	61.8 (62.7)	--	78.4 (63.6)	--	103.0 (83.9)	--
Median	58.0	--	57.0	--	61.0	--
Min, max	1, 169	--	1, 176	--	10, 334	--

- Elevated transaminase events were coded using MedDRA version 22.1.
- Events/100PY: number of events per 100 patient years (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100PY.
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- When summarizing number of subjects with related (serious) events, events with relationship of related, possibly related, and missing are counted.
- The duration was only calculated for the events with complete start and end dates; the time-to-onset was only calculated for the events with complete start date.
- Preferred Terms are sorted by alphabetical order.

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Cumulative Safety Set

Ten (2.0%) subjects discontinued VX-445/TEZ/IVA due to AEs, with 4 (0.8%) subjects discontinuing due to LFT elevations and 2 (0.4%) subjects discontinuing due to rash events.

Subjects who received VX-445/TEZ/IVA for at least 48 weeks

Elevated transaminase AEs occurred in 36 (13.3%) subjects, no events were serious.

Laboratory elevations in ALT and/or AST >3 ×, 5 ×, and >8 × ULN occurred in 30 (11.1%) subjects, 7 (2.6%) subjects, and 4 (1.5%) subjects. No subjects had elevations of ALT or AST >3 × ULN concurrent with a newly occurring elevation in total bilirubin >2 × ULN. Three (1.1%) subjects had ALT or AST >3 × ULN and total bilirubin >2 × ULN during Studies 102 or 105; in 2 subjects, the elevations were not concurrent. The third subject had a medical history of Gilbert's syndrome and an elevated total bilirubin at screening >2 × ULN that remained high throughout the study.

Pooled Analysis of Phase 1 Studies in Healthy Subjects

No subjects had transaminase elevation events. There were no trends in mean ALT or AST in the Phase 1 studies. In the Any VX-445 group, 1 (0.5%) subject had AST >3 × to ≤5 × ULN at the Safety Follow-up Visit.

Bilirubin Elevation Events

Blood bilirubin is a substrate of OATP1B1 and OATP1B3, and VX-445 is an OATP1B1 and OATP1B3 inhibitor based on *in vitro* results; as such, blood bilirubin levels could be increased with VX-445/TEZ/IVA treatment.

Study 102 Safety Set

AEs of bilirubin elevation occurred in 10 (5.0%) subjects in the VX-445/TEZ/IVA group and 2 (1.0%) subjects in the placebo group.

None of the AEs of bilirubin elevation were serious or led to treatment discontinuation. One subject in the VX-445/TEZ/IVA group had an AE of blood bilirubin increased that led to treatment interruption; the AE resolved, and study drug was resumed.

Increases from baseline in mean total bilirubin (up to 4.0 µmol/L) were observed in the VX-445/TEZ/IVA group, with a greater increase in indirect bilirubin (up to 2.7 µmol/L) than in direct bilirubin (up to 1.3 µmol/L; Study 102 CSR/Table 14.3.4.1); however, the mean values of the 3 bilirubin parameters were within normal range throughout the study. The bilirubin elevation was observed at Day 15 and remained at a similar level for the rest of the study. In the placebo group, changes from baseline in mean total bilirubin were minimal.

The majority of subjects had bilirubin values that remained within the normal range. In the VX-445/TEZ/IVA group, 8 (4.0%) subjects had elevations in total bilirubin >2 × ULN of which one subject >2 × ULN. Threshold analyses for direct bilirubin and indirect bilirubin showed a similar pattern of elevations with that observed in the mean value analyses. In the placebo group, 1 (0.5%) subject had elevations in total bilirubin >2 × ULN.

Study 103 Safety Set

No subjects had AEs of bilirubin elevation. Increases from baseline in mean total bilirubin were observed in the VX-445/TEZ/IVA group with a greater increase in indirect bilirubin than in direct bilirubin; however, the mean values of the 3 bilirubin parameters were within normal range throughout the study. The greatest mean (SD) change in total bilirubin (3.0 (2.9) µmol/L) was observed at Week 4, compared to placebo -0.6 (2.3) µmol/L.

Study 105 Safety Set

AEs of bilirubin elevation occurred in 23 (4.5%) subjects. Nineteen (3.8%) subjects had elevations in total bilirubin >2 × ULN. Threshold analyses for other bilirubin parameters showed a similar pattern of elevations with that observed in the VX-445/TEZ/IVA group of Study 102: the incidence of >2 × ULN elevations was higher for indirect bilirubin (26 subjects [5.1%]) than direct bilirubin (1 subject [0.2%]). Overall, the bilirubin data in Study 105 were consistent with those in the parent studies (Studies 102 and 103).

In the Pooled Analysis of Phase 1 Studies in Healthy Subjects, no subjects had AEs of bilirubin elevation. Increases in mean total bilirubin were observed in 2 of the Phase 1 studies in healthy subjects, with a greater increase in indirect bilirubin than in direct bilirubin.

Rash Events

In the Phase 1 DDI study in healthy female subjects taking VX-445/TEZ/IVA and oral hormonal contraceptives (Study 002), 4 of 15 subjects (26.7%) had a rash event. Therefore, rash was considered an event of special interest in the Phase 3 studies.

The Treatment-emergent Rash Events in Study 102 Safety Set, and Study 105 IA2 Safety Set (OLE) are presented in Table 41. The details are provided per safety set.

Study 102 Safety Set

Twenty-two (10.9%) subjects in the VX-445/TEZ/IVA group and 13 (6.5%) subjects in the placebo group had a least 1 rash event. The majority of events were mild or moderate in severity. One (0.5%) subject in the VX-445/TEZ/IVA group had a rash event that led to treatment discontinuation. Four (2.0%) subjects in the VX-445/TEZ/IVA group and 1 (0.5%) subject in the placebo group had events that led to treatment interruption; all resumed treatment.

Serious rash events occurred in 3 (1.5%) subjects in the VX-445/TEZ/IVA group (2 SAEs of rash, 1 SAE of rash pruritic), of which 2 events were considered treatment related; all events resolved. In the placebo group, 1 (0.5%) subject had a serious rash event.

The median time to onset of first rash event was 13.5 days (range: 5, 157) in the VX-445/TEZ/IVA group and 27.0 days (range: 1, 157) in the placebo group. The median duration of rash events was 7.0 days (range: 1, 92) in the VX-445/TEZ/IVA group and 8.0 days (range: 2, 61) in the placebo group.

The incidence of rash events was higher in females than in males in both treatment groups. In the VX-445/TEZ/IVA group, 16 (16.3%) female subjects and 6 (5.8%) male subjects had rash events. In the placebo group, 8 (8.3%) female subjects and 5 (4.8%) male subjects had rash events.

In female subjects receiving VX-445/TEZ/IVA, 8 (20.5%) subjects who used hormonal therapy during the study and 8 (13.6%) subjects not using hormonal therapy had rash events. In female subjects receiving placebo, 3 (9.4%) subjects who used hormonal therapy during the study and 5 (7.8%) subjects not using hormonal therapy had rash events.

Of the 8 subjects in the VX-445/TEZ/IVA group who used hormonal therapy and had a rash event, 1 subject had a rash event before beginning hormonal therapy use; 4 subjects had no changes to study drug or hormonal therapy, and the rash resolved; 2 subjects had VX-445/TEZ/IVA treatment interruptions, discontinued hormonal therapy, and resumed study drug after the rash resolved; and 1 subject remained on hormonal therapy and discontinued VX-445/TEZ/IVA treatment, and the rash resolved.

Study 103 Safety Set

In the VX-445/TEZ/IVA group, 2 (3.6%) subjects had a rash event; both were female. One rash event occurred in a subject who had concomitant use of hormonal therapy; this event was considered serious and possibly related to study drug. The subject discontinued use of OCs and continued study drug treatment, and the rash resolved.

In the TEZ/IVA group, 2 (3.8%) subjects had a nonserious rash event; both were female, and 1 subject had concomitant use of hormonal therapy.

All rash events were mild in severity, and none led to treatment discontinuation or interruption.

Study 105 Safety Set

In Study 105, in IA2 50 (9.9%) subjects had rash events. The rash events were exanthematous and mostly mild to moderate in severity. A serious rash event occurred in 1 (0.2%) subject; study drug was discontinued, and the event resolved. Five (1.0%) subjects had rash events that led to treatment interruption.

The incidence of rash events was higher in females than in males: 27 (10.8%) female subjects and 23 (9.0%) male subjects had rash events. Of the 94 female subjects taking hormonal therapy during the study, 12 (12.8%) had rash events; of the 157 female subjects not taking hormonal therapy during the study, 15 (9.6%) had rash events. Overall, the nature and severity of the rash events in Study 105 were consistent with those in the parent studies (Studies 102 and 103).

Table 41 Summary of AESI: Treatment-emergent Rash Events - Study 102 Safety Period, OL Safety Period

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any events	13 (6.5)	17.01	22 (10.9)	29.95	50 (9.9)	15.77
Subjects with any events by maximum severity						
Mild	10 (5.0)	--	17 (8.4)	--	33 (6.5)	--
Moderate	3 (1.5)	--	4 (2.0)	--	16 (3.2)	--
Severe	0	--	1 (0.5)	--	1 (0.2)	--
Life-threatening	0	--	0	--	0	--
Missing	0	--	0	--	0	--
Subjects with events leading to treatment discontinuation	0	0	1 (0.5)	1.00	1 (0.2)	0.25
Subjects with events leading to treatment interruption	1 (0.5)	1.00	4 (2.0)	3.99	5 (1.0)	1.27
Subjects with serious events	1 (0.5)	1.00	3 (1.5)	2.99	1 (0.2)	0.25
Subjects with related serious events	0	0	2 (1.0)	2.00	1 (0.2)	0.25
Subjects with events leading to death	0	0	0	0	0	0

- Rash events were coded using MedDRA version 22.1.
- Events/100PY: number of events per 100 patient years (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100PY.
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- When summarizing number of subjects with related (serious) events, events with relationship of related, possibly related, and missing are counted.
- The duration was only calculated for the events with complete start and end dates; the time-to-onset was only calculated for the events with complete start date.
- Preferred Terms are sorted by alphabetical order.

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Safety in subjects who received VX-445/TEZ/IVA for at least 48 weeks

In IA2, rash events occurred in 42 (15.5%) subjects; these events were generally exanthematous rashes and mostly mild (32, 11.8%) to moderate (9, 3.3%) in severity. The exposure-adjusted event rate for rash events was lower in this subset of subjects in Study 105 than in the Study 102 VX-445/TEZ/IVA group (18.90 versus 29.95 events/100PY). Three (1.1%) subjects had rash events that were serious. Four (1.5%) subjects had rash events that led to treatment interruption.

Pooled Analysis of Phase 1 Studies in Healthy Subjects

In the Any VX-445 group, 7 (3.7%) subjects had rash events, of whom 2 (1.0%) subjects discontinued study drug due to a rash event. All rash events were mild or moderate in severity and nonserious. The median time to onset of rash events was 11.0 days (range: 10 to 19 days).
Of the 7 subjects who had rash events in the Any VX-445 group, 4 were female subjects from Study 002 (OC DDI), and 3 were male subjects. The incidence of rash events in female subjects in Study 002 was 4 of 15 subjects (26.7%).

In the placebo group, 1 (1.9%) subject had 2 rash events of dermatitis. The time to onset of the first event was 9 days.

CK Elevation Events

Study 102 Safety Set

AEs of CK elevation occurred in 20 (9.9%) subjects in the VX-445/TEZ/IVA group (18 with AEs of blood creatine phosphokinase increased, 1 with an AE of rhabdomyolysis, and 1 with both AE) and 9 (4.5%) subjects in the placebo group (9 with AEs of blood creatine phosphokinase increased and 1 also with an AE of rhabdomyolysis). The majority of subjects with CK elevation events had asymptomatic laboratory elevations, many of which were preceded by exercise. The AEs were mostly mild or moderate; AEs were of severe intensity in 5 subjects in the VX-445/TEZ/IVA group and no subjects in the placebo group. One subject in the VX-445/TEZ/IVA group had an SAE of CK elevation (rhabdomyolysis).
The 2 subjects in the VX-445/TEZ/IVA group with AEs of rhabdomyolysis presented with CK elevations, and neither subject had clinical features of rhabdomyolysis (e.g., kidney involvement, myoglobinuria). Before event onset, both subjects had performed strenuous exercise (power lifting and CrossFit). Both subjects resumed treatment following interruption. The 1 subject in the placebo group with an AE of rhabdomyolysis had increased CK as well as elevated blood myoglobin. Narratives for subjects who had AEs of rhabdomyolysis are provided.
AEs of CK elevation led to study drug interruption in 3 subjects in the VX-445/TEZ/IVA group and no subjects in the placebo group. Most AEs of CK elevation in both treatment groups resolved without change to study drug dosing or after treatment interruption. No subjects discontinued treatment due to AEs of CK elevation in either treatment group.

The mean CK concentration was variable over time in both groups. In the VX-445/TEZ/IVA group, increases from baseline in mean CK were observed. The mean (SD) increases in CK ranged from 35.9 (245.6) U/L at Week 12 to 108.2 (650.2) U/L at Week 24. In the placebo group, there were no trends in CK.

The majority of subjects had CK levels that remained within the normal range. Twenty-one (10.4%) subjects in the VX-445/TEZ/IVA group had CK >5 × ULN, including 10 (5.0%) subjects with CK >10 × ULN. Ten subjects (5.0%) in the placebo group had CK >5 × ULN, including 3 subjects (1.5%) with CK >10 × ULN. The majority of subjects with elevations >10 × ULN had exercised before the elevations.

Study 103 Safety Set

No subjects had AEs of CK elevation.

Increases from baseline in mean and median CK were observed in the VX-445/TEZ/IVA group. The greatest mean (SD) change (22.6 [171.0] U/L) was observed at Day 15.

Study 105 Safety Set

In Study 105, AEs of CK elevation occurred in 31 (6.1%) subjects, none of whom had AEs of rhabdomyolysis. The exposure-adjusted event rate for AEs of CK elevation was lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group (8.90 versus 19.96 events/100PY)

The AEs were mostly mild or moderate in severity. One subject had a serious CK elevation event following strenuous exercise, and the SAE resolved without changes to study drug dosing. Four (0.8%) subjects had an AE of CK elevation that led to treatment interruption, and no subjects discontinued treatment due to AEs of CK elevation.

The majority of subjects had CK levels that remained within the normal range. Forty-two (8.3%) subjects had CK >5 × ULN, including 16 (3.2%) subjects with CK >10 × ULN.

Most subjects with CK elevations had asymptomatic laboratory elevations, many of which were preceded by exercise.

Laboratory findings

Haematology and Coagulation

Mean concentrations of haematology parameters were variable over time in both groups. In the VX-445/TEZ/IVA group, decreases from baseline in mean platelets, leukocytes, and neutrophils were observed; however, mean values of all 3 parameters remained within normal limits at all assessed time points. These findings are not considered clinically adverse and may be markers of reduced systemic inflammation. There were no trends observed in other haematology parameters in either the VX-445/TEZ/IVA or placebo group in study 102 or the VX-445/TEZ/IVA group in study 103. There were no trends in coagulation assessments in either group of both studies 102 and 103.

AEs related to haematology and coagulation were infrequent; none of the AEs were serious or led to treatment discontinuation or interruption.

Other Serum Chemistry

Selected serum chemistry laboratory assessments are discussed in events of specific interest There were no trends in other chemistry parameters. Overall, AEs related to other chemistry parameters were infrequent and had a similar overall incidence between treatment groups. None of these AEs were serious or led to treatment discontinuation, and none led to treatment interruption in the VX-445/TEZ/IVA group.

Urinalysis

There were no trends observed in the urinalysis results.

Vital Signs

In Study 102, increases from baseline in mean BP parameters were observed in the VX-445/TEZ/IVA group; increases from baseline ranged from 2.0 to 3.5 mm Hg for mean SBP and 1.1 to 1.9 mm Hg for mean DBP, without a trend of continued increase during the study. The proportion of subjects who had BP in the hypertensive range (i.e., SBP >140 mm Hg or DBP >90 mm Hg) on at least 2 occasions was

similar between the treatment groups. There were few AEs of BP increase (1 subject in the VX-445/TEZ/IVA group and 2 subjects in the placebo group). Given the similar incidence of subjects in the hypertensive range between treatment groups and occurrence of few AEs, the modest increase in mean BP in this normotensive population is unlikely to be clinically relevant. There were no meaningful changes in BP in Study 103 or the Phase 1 studies in healthy subjects.

In study 105, for subjects who received VX-445/TEZ/IVA in Study 102, there was no further increase in mean BP with continued VX-445/TEZ/IVA treatment in Study 105. For subjects who received placebo in Study 102 and received VX-445/TEZ/IVA in Study 105, the increase in mean BP was generally similar to that observed in the VX-445/TEZ/IVA group in Study 102. Few subjects (5 [1.0%] subjects) in Study 105 had AEs of increased BP; all AEs were mild in severity, and none required study drug interruption or discontinuation.

In Studies 102 and 103, decreases from baseline in mean pulse rate (up to 4.3 bpm in Study 102 and up to 5.5 bpm in Study 103) were observed in the VX-445/TEZ/IVA group. No subjects had AEs of decreased HR. The decrease in mean pulse rate is not considered to be clinically relevant. There were no meaningful changes in pulse rate in the Phase 1 studies in healthy subjects.

In IA2, there were also 83 subjects that had tachycardia with >100 beats per minute. Among these subjects, tachycardia was accompanied by an increase of heartrate > 20 beats/min in 22 subjects.

In all studies, there were no trends in temperature, respiratory rate, or pulse oximetry.

Electrocardiogram Data

In Studies 102 and 103, decreases from baseline in mean HR were observed in the VX-445/TEZ/IVA group. In study 102, the mean (SD) decreases in HR ranged from -3.7 (12.3) bpm at Week 16 to -5.8 (12.4) bpm at 2 hours post-dose on Day 15. In the placebo group, changes from baseline in mean HR were minimal. In study 103, the greatest mean (SD) change in the VX-445/TEZ/IVA group (-5.4 [8.8] bpm) was observed at Week 4 (compared to 1.9 [9.3] bpm in the TEZ/IVA group).

AEs related to ECG findings or relevant cardiac disorders were infrequent with a similar overall incidence across treatment groups. None of the AEs related to ECG findings or relevant cardiac disorders were serious or led to treatment discontinuation or interruption.

High-precision QT analysis (in Study 001) and a thorough QT/QTc study (Study 009) were conducted for VX-445 and its metabolite M23-445. Both studies showed a lack of effect of VX-445 on QTc.

In separate thorough QT studies for the TEZ and IVA clinical development programs (Studies 661-010 and 770-008, respectively), TEZ and IVA did not prolong the QT/QTc interval in healthy subjects to any clinically relevant extent at doses up to 3 times the maximum recommended dose.

Post-dose Spirometry

Post-dose spirometry was assessed in healthy subjects at approximately 6 hours post-dose on Days 1 and 9 in Study 001 (Parts B and C), and in CF subjects at 5 hours post-dose on Days 1 and 15 in Study 001 (Parts D, E, and F). There were no clinically relevant decreases in post-dose spirometry. Overall, the post-dose $ppFEV_1$ values showed no evidence of decline from the pre-dose $ppFEV_1$ at any assessment time points for both healthy and CF subjects.

Ophthalmologic Examinations

Due to nonclinical findings of cataracts/lens opacities in a study involving IVA monotherapy and the implementation of recommended ophthalmologic examinations in paediatric patients treated with IVA, ophthalmologic examinations were performed in the VX-445 clinical program in subjects <18 years of age.

In Study 102, one (0.5%) subject in the VX-445/TEZ/IVA group had AEs of cataract cortical and lenticular opacity; this subject had a history of CF-related diabetes and concomitant use of corticosteroids. One (0.5%) subject in the placebo group had an AE of cataract; this subject had concomitant use of corticosteroids. Both AEs were mild in severity, not clinically significant, and did not require treatment or lead to interruption or discontinuation of study drug. In Study 103, follow-up ophthalmologic examinations were not required given the short study duration.

Overall, the ophthalmological examination (OE) data are consistent with previous experience with IVA and IVA-containing regimens.

Safety in special populations

A summary of the safety profile of subjects in subgroups of F508del-CFTR mutation with F/MF and F/F in the cumulative safety data across Studies 102, 103, and 105. Across the F/MF and F/F subgroups, the majority of AEs were mild to moderate in severity, and most were consistent with common manifestations of cystic fibrosis (CF) disease or with common illnesses in CF subjects 12 years of age and older. The most common AEs (incidence of ≥15% of subjects in any subgroup) were similar across the F/MF and F/F subgroups. Overall, the safety results were similar between the F/MF and F/F subgroups, and no new safety concerns were identified.

The safety profile is generally also similar across subgroups of patients, including sex, ppFEV1, geographic regions, and genotypes.

The safety results were generally consistent in the subgroups subjects ≥18 years of age and subjects ≥12 to <18 years of age. There were no patients > 65 year in study 102 or study 103.

Immunological events

In Study 102, 4 (2.0%) subjects in each group had an immunological event. In Study 105 IA2, 22 (4.3%) subjects had AEs in the immune system disorders SOC, mainly associated with external allergens (e.g., environmental, animal, food) and were not considered study drug-related. One subject had a nonserious AE of anaphylactic reaction that was caused by an allergic reaction to cashews. The event resolved without change to study drug dosing and was assessed by the investigator as not related to study drug.

Table 42 AEs in the SOC of Immune System Disorders Occurring in At Least 1 Subject: Study 102 Safety Period, OL Safety Period, and Cumulative TC Safety Period (Study 102 Safety Set, OL Safety Set, and Cumulative TC Safety Set)

	Study 102		Study 105 (OLS)	Cumulative TC Safety Period
Preferred Term, n (%)	Placebo in 445-102 N = 201	VX-445/TEZ/IVA in 445-102 N = 202	Any VX-445/TEZ/IVA N = 506	Any VX-445/TEZ/IVA N = 510
Subjects with at least 1 AE in immune system disorders SOC	4 (2.0)	4 (2.0)	22 (4.3)	26 (5.1)
Seasonal allergy	2 (1.0)	3 (1.5)	16 (3.2)	19 (3.7)
Hypersensitivity	1 (0.5)	1 (0.5)	2 (0.4)	3 (0.6)
Drug hypersensitivity	1 (0.5)	0	2 (0.4)	2 (0.4)
Allergy to animal	0	0	1 (0.2)	1 (0.2)
Allergy to arthropod bite	0	0	1 (0.2)	1 (0.2)
Anaphylactic reaction	0	0	1 (0.2)	1 (0.2)
Food allergy	0	0	1 (0.2)	1 (0.2)

Source: ISA2 Table 2.3.1.2.1

AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; OLS: open-label study; PT: Preferred Term; SOC: System Organ Class; TC: triple combination; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency of the Any VX-445/TEZ/IVA column during the Cumulative TC Safety Period by PT.

Safety related to drug-drug interactions and other interactions

No information on PD interactions is provided. For PK interactions, please refer to clinical pharmacology discussion for pharmacokinetic interactions (CYP3A inducer/inhibitor interactions).

Discontinuation due to adverse events

In Study 102, two subjects (both in the VX-445/TEZ/IVA group) discontinued study drug due to an AE, one subject with a non-serious AE of rash and one subject with a medical history of hepatic cirrhosis because of a SAE of portal hypertension. Both events were assessed by the investigator as being of moderate severity and possibly related to study drug.

In Study 103, no subjects had AEs that led to treatment discontinuation.

In IA2 of Study 105, 7 (1.4%) subjects had AEs that led to treatment discontinuation. Three subjects discontinued due to AEs of transaminase elevation. The other subjects discontinued treatment due to AEs of depression (1 subject), rash (1 subject), tinnitus and contusion (1 subject) and hepatic encephalopathy (1 subject). For the subject with non-serious AEs of tinnitus and contusion, study drug was discontinued, and the events were ongoing at time of the data cut. For the other subjects the AE were resolved after discontinuation of study drug. For the subject who discontinued VX-445/TEZ/IVA treatment due to an SAE of hepatic encephalopathy the event resolved with treatment. The subject had a history of hepatic cirrhosis, portal hypertension with gastric varices, and thrombocytopenia.

In the Cumulative Safety Set, 10 (2%) subjects discontinued study drug due to AEs, with 4 (0.8%) subjects discontinuing due to LFT elevations and 2 (0.4%) subjects discontinuing due to rash events.

In the set of subjects who received VX-445/TEZ/IVA for at least 48 weeks, none of the subjects were discontinued from study medication.

In the Healthy Subjects, in the Any VX-445 group, 2 (1.0%) subjects had AEs that led to treatment discontinuation, both of which were rash events. One subject with rash generalized who received VX-445 in Study 009, a thorough QT/QTc study and one subject with dermatitis who received VX-445/TEZ/IVA in Study 001, a single- and multiple-dose escalation first-in-human study.

AEs Leading to Interruption of Study Drug

In Study 102, 29 subjects (19 subjects [9.4%] in the VX-445/TEZ/IVA group and 10 subjects [5.0%] in the placebo group) interrupted study drug due to an AE. Of the 19 subjects in the VX-445/TEZ/IVA group, 16 subjects resumed study drug treatment in Study 102, and 3 subjects enrolled in extension Study 105 while study drug was interrupted.
In the VX-445/TEZ/IVA group, AEs that led to treatment interruption that occurred in ≥2 subjects were rash, ALT increased, infective PEx of CF, influenza, and rhabdomyolysis. In the placebo group, ALT increased led to treatment interruption in ≥2 subjects.

In Study 103, no subjects had AEs that led to treatment interruption.

In Study 105, 29 (5.7%) subjects had AEs that led to treatment interruption. Events that occurred in≥2 subjects were ALT increased, AST increased, rash, blood alkaline phosphatase increased, GGT increased, and blood creatinine phosphokinase increased. Other AEs that lead to interruption were pruritus generalised, abdominal pain upper, constipation, duodenitis, gastric haemorrhage, cholecystitis acute, depression blood bilirubin increased, liver function test increased, pityriasis rosea, rash maculo-papular, infective pulmonary exacerbation of cystic fibrosis, bacterial vaginosis, hand-foot-and-mouth disease, tendonitis, pulmonary haemorrhage, pyrexia, burning sensation, haematuria..

Post marketing experience

IVA monotherapy was first authorized globally in the US on 31 January 2012 for the treatment of CF and was subsequently authorized in multiple countries globally. Cumulatively worldwide as of 02 September 2019, 6,511 patients (representing 17,817 person-years) were exposed to IVA in the post marketing setting.

TEZ/IVA was first authorized globally in the US on 12 February 2018 for the treatment of CF and was subsequently authorized in multiple countries globally. Cumulatively worldwide as of 11 August 2019, 9,652 patients (representing an estimated 6,538 person-years) were exposed to TEZ/IVA in the post marketing setting.

Overall, the post marketing experience for both IVA and TEZ/IVA remains consistent with the safety profiles for each product that were established in clinical studies.

2.5.1. Discussion on clinical safety

Patient population and exposure

The core safety analyses in CF subjects evaluated data from Studies 102 and 103, and an interim analysis (IA2) of the open-label extension Study 105 as separate sets. Study 102 provided the main safety data. In addition to the core safety analyses, a Cumulative Safety Set and a subset of subjects in the Cumulative Safety Set who received ≥ 48 weeks of treatment with VX-445/TEZ/IVA were presented. Overall, these sets provide a sufficient overview of the safety. Study 105 is ongoing (IA1 cut-off date 10 July 2019, IA2 cut-off date 31 October 2019). Further safety data will be provided post approval which was considered acceptable by CHMP.

In the Phase 3 program, 510 subjects received at least 1 dose of VX-445/TEZ/IVA, with a total exposure of approximately 496.6 patient-years. In the Cumulative Safety Set (parent Studies 102 or 103 and/or during Study 105), 12 subjects had an exposure of ≤ 24 weeks, 229 subject > 24 ≤ 48 weeks, and 271 subjects ≥ 48 weeks. This is considered sufficient to assess long-term safety.

Adverse events, serious adverse events and deaths

Pivotal placebo-controlled studies (Study 102 and Study 103)

Nearly all patients in both arms in study 102 experienced at least one treatment-emergent AE (93.1% of patients in the VX-445/TEZ/IVA arm and 96.0% in the placebo arm). In study 103, these numbers are much lower, 58.2% in the VX-445/TEZ/IVA group and 63.5% in the TEZ/IVA group, likely because of the shorter duration of this study.

Overall, the AEs were mostly consistent with common manifestations of CF disease or with common illnesses. In study 102, AEs occurring in ≥8% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group were headache (17.3% versus 14.9%), diarrhoea (12.9% versus 7.0%), upper respiratory tract infection (11.9% versus 10.9%), abdominal pain (9.9% versus 6.0%), alanine transaminase (ALT) increased (9.9% versus 3.5%), aspartate transaminase (AST) increased (9.4% versus 2.0%), blood creatine phosphokinase increased (9.4% versus 4.5%), nasal congestion (9.4% versus 7.5%), rash (8.9% versus 4.5%), and rhinorrhoea (8.4% versus 3.0%). All of these are included as ADRs in section 4.8 of the SmPC.

Initially AEs occurring in ≥8% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group were considered an ADR. However, this margin was considered arbitrary and generous. Upon request by CHMP, additional analyses with more stringent margins were provided. Two additional ADRs occurred in ≥5% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher

than in the placebo group compared to the cut-off level of ≥8%, i.e. rhinitis and influenza. Compared to the cut-off level of >5%, 8 additional ADRs occurred in ≥3% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group, i.e., abdominal pain upper, flatulence, hypoglycaemia, acne, dizziness, pruritus, wheezing and abnormal breathing. All of these have been included in section 4.8 of the SmPC as ADRs. Blood pressure increased is also included in section 4.8 of the SmPC as an ADR.

Results in Study 103 were reasonably similar to results in the study 102 Safety set. In Study 103, the incidence of subjects with at least 1 AE was lower than in Study 102 but similar in both treatment groups (58.2% in the VX-445/TEZ/IVA group and 63.5% in the TEZ/IVA group). The different duration of the studies is likely the reason for the differences in incidence of AEs.

In Study 102, related AEs occurred more frequently in the VX-445/TEZ/IVA (47.5%) compared to the placebo group (25.9%). These most frequent related in order of highest frequency are sputum increased (6.9%) ALT increased (5.9%), AST increased (5.4%) and rash (5.4%). These related AEs are also more frequent than in placebo. In study 103 Safety Set, more subjects in the VX-445/TEZ/IVA group (12 (21.8%)) had related AEs compared subjects in the placebo group (9 (17.3%)). The most frequent related in order of highest frequency was respiration abnormal (5.5%) while all other events were only observed in 1 or 2 patients.

Overall the numbers of Grade 3 or 4 AEs were low. In study 102, 19 (9.4%) subjects had severe AEs and no subjects had life-threatening AEs in the VX-445/TEZ/IVA group, while 14 (7.0%) subjects had severe AEs and 1 (0.5%) subject had a life-threatening AE of neuroglycopenia in the placebo group. Blood creatine phosphokinase increased (2%) and alanine aminotransferase increased (1%) and aspartate aminotransferase increased (1%) occurred ≥ 1%. In the Study 103 Safety Set, only 1 (1.9%) subject in the TEZ/IVA group had a severe AE (musculoskeletal pain).

Eight cases of haemoptysis were classified as possibly related to study drug all in patients treated with VX-445/TEZ/IVA. Of note, an additional case of severe gastric haemorrhage (unlikely related) was reported. Two additional cases, one each of ocular retrobulbar haemorrhage (possibly related), menorrhagia (possibly related) and 3 cases of vaginal haemorrhage (not related) were reported. There were no clear markers of increased tendency to bleed. There was no evidence of increased prothrombin times, platelets decreased were reported in 6.7% of subjects but no subjects reported decreases ≥25 to <50 (10^9/L). Thus, no PI update was deemed necessary at this stage.

The event rate for influenza was 3E/100PY in the placebo arm and 16E/100PY in VX-445/TEZ/IVA arm in Study 102, while it was 4.6E/100PY and 6.9E/100PY in the long term OLS and Cumulative safety analyses respectively. The difference between placebo arm and in VX-445/TEZ/IVA arm in Study 102 is not sufficiently explained. On the basis of this analysis, and also taking into consideration the analysis of AEs occurring in ≥5%, and ≥3% of subjects, Influenza is included as an ADR in section 4.8 in Kalydeco SmPC. The MAH committed to monitoring reporting rates of influenza in subsequent PSURs.

In study 102, the incidence of SAEs was lower in VX-445/TEZ/IVA group (28 (13.9%)) than in the placebo group (42 (20.9%)). Overall, the SAEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects. Rash and influenza occurred in ≥2 subjects in any group and were more common in the VX-445/TEZ/IVA group than the placebo group. In study 103, 1 subject had an SAE of infective pulmonary exacerbation (PEx) of CF and 1 subject had an SAE of rash in VX-445/TEZ/IVA group while 1 (1.9%) subject had an SAE of infective PEx of CF in the TEZ/IVA group.

No deaths were reported in the VX-445/TEZ/IVA clinical development program.

Long term open-label safety study, Study 105 Safety Set, Cumulative safety Set and safety in patients who received VX-445/TEZ/IVA for at least 48 weeks

The long-term safety Study 105 Safety Set and Cumulative safety Set showed decreased incidences of (related) AEs, Grade 3-4 AEs, SAEs and AEs leading to treatment discontinuation with VX-445/TEZ/IVA compared to Study 102 Safety Set.

The (related) AEs and SAE were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older. A total of 169 (33.4%) subjects had AEs considered related or possibly related to VX-445/TEZ/IVA. In addition to already observed related AE in study 103, photosensitivity reaction was observed in 7 subjects, but all resolved with continued study drug treatment. Furthermore, the exposure-adjusted event rate for the AE of photosensitivity reaction overall was similar in Study 105 and in the placebo group of Study 102. Taking these arguments into account there is insufficient information to include photosensitivity as and ADR. Nevertheless, photosensitivity will be reviewed in subsequent PSURs.

The exposure-adjusted event rates for the majority of AEs were similar or lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group apart from cough, fatigue, haemoptysis and sinus congestion that occurred more frequently in Study 105.

In Study 105, 51 (10.1%) subjects had severe (Grade 3) AEs and 2 (0.4%) subjects had life-threatening (Grade 4) AEs. Only pulmonary exacerbation of cystic fibrosis (3.2%) occurred >1% as Grade 3 and 4 AE. The two life-threatening AEs were an event of non-related suicide attempt and an event pulmonary haemorrhage, which was considered to be possibly related to VX-445/TEZ/IVA.

In both the overall cumulative analysis and the 48-week cumulative exposure analysis, Exposure-adjusted analyses of event rates in Study 102 showed a decrease in the rates of the majority of related AEs with longer-term treatment compared with Study 105.

In the set of subjects who receive VX-445 for at least 48 weeks, 41 (15.1%) subjects had at least 1 AE that was Grade 3 or 4 in severity. Grade 3 or 4 events that occurred in ≥2 subjects were infective PEx of CF (10 subjects), blood creatine phosphokinase increased (8 subjects), DIOS (4 subjects), AST increased (4 subjects), ALT increased (3 subjects), GGT increased (2 subjects), gastritis (2 subjects), and influenza (2 subjects).

The safety profile of subjects in subgroups of *F508del-CFTR* mutation with F/MF and F/F in the cumulative safety set was broadly comparable across the F/MF and F/F subgroups respectively.

Adverse events of special interest

Transaminase elevations are common in CF and have been observed in patients receiving IVA monotherapy, TEZ/IVA, and VX-445/TEZ/IVA. In the pivotal VX-445/TEZ/IVA, exclusion criteria for patients with pre-existing liver function impairments were more stringent compared to the Orkambi and Symkevi clinical studies. In the VX-445/TEZ/IVA studies, patients were excluded when 1 out of the defined impairments were present instead of 2 (Symkevi) or 3 (Orkambi) trial.

In Study 102, the incidence of transaminase elevation adverse events was 2-3 times higher in the VX-445/TEZ/IVA group than in the placebo group. The vast majority of the events were non-severe, non-serious and did not lead to treatment discontinuation. In addition, only one event of portal hypertension in the VX-445/TEZ/IVA was a SAE, occurring in a subject with a history of hepatic cirrhosis, that led to discontinuation of VX-445/TEZ/IVA treatment.

Results from Study 103 and Study 105 were generally consistent with those from Study 102. In addition, increases from baseline in mean total bilirubin were observed in the VX-445/TEZ/IVA group, with a greater increase in indirect bilirubin than direct bilirubin. In the placebo group, changes from baseline in mean total bilirubin were minimal. AEs associated with bilirubin elevation occurred in 10 (5.0%) subjects in the VX-445/TEZ/IVA group and 2 (1.0%) subjects in the placebo group. One subject had an AE of bilirubin elevation that was not serious and led to treatment interruption. Rash

events have been seen in subjects treated with VX-445/TEZ/IVA including in the Phase 1. In Study 102, there was a higher incidence of rash events in the VX-445/TEZ/IVA group (10.9%, 22 subjects) than in the placebo group (6.5%, 13 subjects). Most rashes occurred within the first 3 weeks of study drug treatment. Serious rash events occurred in 3 (1.5%) subjects in the VX-445/TEZ/IVA group, while in 1 (0.5%) subject in the placebo group. There was also an increase in the incidence of rash in female subjects taking hormonal therapy compared with those not taking hormonal therapy; the increase was larger in the VX-445/TEZ/IVA group than in the placebo group. Therefore, a role for hormonal therapy in the occurrence of rash cannot be excluded. This has been adequately addressed in section 4.4 of the SmPC.

AEs of CK elevation occurred more frequently in subjects in the VX-445/TEZ/IVA group compared to the placebo group. The majority were asymptomatic laboratory elevations, many of which were preceded by exercise. Most AEs of CK elevation resolved without change to study drug dosing or after treatment interruption. The 2 subjects in the VX-445/TEZ/IVA group with AEs of rhabdomyolysis presented with CK elevations, and neither subject had clinical features of rhabdomyolysis (e.g., kidney involvement, myoglobinuria). Both subjects had performed strenuous exercise (power lifting and CrossFit), which was likely the cause of the CK elevations. A warning regarding increased CK is included in section 4.8 of the SmPC.

No clinically meaningful trends in the respiratory-related AEs or postdose spirometry data were observed during phase I in healthy volunteers and CF patients at the proposed dose.

In Study 102, small increases from baseline in SBP and DBP were observed in the VX-445/TEZ/IVA group were observed. This has been adequately captured in section 4.8 of the SmPC.

Safety in special populations

No patients in the Phase 3 clinical studies were aged 65 years or older at screening. This is acceptable when considering the severity of the disease and life-expectancy in the investigated CF mutations (homozygote F508del and heterozygote F508del/MF).

The safety profile of Kaftrio in combination with Kalydeco is generally also similar across subgroups of patients, including sex, ppFEV1, geographic regions, and genotypes.

Assessment of paediatric data on clinical safety

No clinically relevant differences in safety profile of VX-445/TEZ/IVA between patients ≥12 to <18 years of age and ≥18 years of age have been observed.

2.5.2. Conclusions on clinical safety

The safety profile of Kalydeco alone and in combination therapy with other CFTR modulators is sufficiently characterised with extensive post marketing experience.

Additionally, the clinical studies submitted for the extension of indication of Kalydeco in association with Kaftrio are adequate.

Overall, the combination treatment of Ivacaftor and Kaftrio was well tolerated with low discontinuation rates due to AEs. In the clinical studies performed with Kaftrio in combination with ivacaftor, an increase in hepatic toxicity, influenza and rash were identified. These safety events have been introduced in the SmPC of Ivacaftor. They can be handled in the clinical practice and have been adequately described in the SmPC.

A warning on the occurrence of rash events is introduced in section 4.4.

The safety profile has been adequately characterised and the safety of Kalydeco in combination with Kaftrio will be further monitored in the PSURs in the post marketing setting

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan.

The PRAC considered that the risk management plan version 8.8 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.8 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	• Hepatotoxicity • Cataract • Concomitant use of IVA with strong CYP3A inhibitors or inducers
Missing information	• Use in pregnant and lactating women • Indicated use in children aged less than 6 years

CYP: cytochrome P450; IVA: ivacaftor

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
None				
Category 3 – Required additional PV activities (by the competent authority)				
Study 126 Ongoing	<u>IVA Arm</u> In subjects with CF who are <24 months of age at treatment initiation and have an approved IVA-responsive mutation: • To evaluate the safety of long-term IVA treatment • To evaluate the PD of long-term IVA treatment	• Hepatotoxicity • Cataract • Use in children aged 12 to <24 months old at initiation	Final Report	March 2022

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	• To evaluate the efficacy of long-term IVA treatment Observational Arm To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have an approved IVA-responsive mutation			

CF: cystic fibrosis; IVA: ivacaftor; PD: pharmacodynamics
Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on monitoring LFTs. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126
Concomitant use of IVA with strong CYP3A inhibitors or inducers	**Routine risk minimisation measure:** SmPC Section 4.2 where dose reductions are recommended when co-administered with a strong inhibitor of CYP3A. SmPC Section 4.4 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only Pregnancy follow-up form **Additional PV activities:** None
Indicated use in children aged less than 6 years	**Routine risk minimisation measure:** SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126

CYP: cytochrome P450, PL: Patient Leaflet; SmPC: Summary of Product Characteristics

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Additionally, minor amendments are introduced in the PI according to QRD template version 10.1.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The package leaflet (PL) for ivacaftor (Kalydeco) was user tested in 2012 (tablets PL) and the 2015 (granules PL).
- A bridging report was submitted and accepted as part of a Type II variation in 2017, after the addition of text relating to co-administration of Kalydeco with Symkevi. This included differences in the indication, advice on co-administration.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. CF is caused by mutations in the CFTR

gene that result in absent or deficient function of the CFTR protein at the cell surface that regulates salt and water absorption and secretion. The failure to regulate chloride results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF.

F508del, is the most common disease-causing mutation (84.7% of the individuals in the US and 81.1% of the individuals in Europe)[2,3]. With the proposed indication, this would result in treatment possibility in a large majority of the patients.

3.1.2. Available therapies and unmet medical need

Two types of CF therapies exist. The use CF therapies that target the symptoms of the disease (such as nutritional supplements, antibiotics, and mucolytics), in combination with CFTR modulators (i.e. correctors and potentiators) is recommended to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life.

Correctors (such as tezacaftor and VX-445), facilitate the cellular processing and trafficking of mutant CFTR to increase the quantity of functional CFTR at the cell surface, resulting in enhanced chloride transport. CFTR potentiators (like ivacaftor) enhance the channel gating activity of the CFTR which is delivered to the cell surface (by correctors).

Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA) and Symkevi (tezacaftor/ivacaftor, TEZ/IVA) are CFTR modulators approved for CF patients with specific mutations.

The initially claimed indication for Kalydeco in combination with Kaftrio was:

"Kalydeco tablets are indicated in a combination regimen with elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene"

The proposed indication covered F/F genotypes, F/MF 'minimal function' genotypes, F/G 'gating' genotypes, and F/RF 'residual function' genotypes. It comprises subpopulations in which approved modulator therapies are available (*F508del* homozygous patients (F/F), patient heterozygous for *F508del* and a specific residual function mutation (F/RF) or a specific gating mutation (F/G). Nevertheless, these treatments do not cure the disease and more efficacious treatments could fulfil the gap in these patients. For the populations heterozygous for *F508del* and a minimal function mutation (F/MF) no treatment is available, which suggests an unmet need in this subpopulation.

3.1.3. Main clinical studies

The main evidence of efficacy and safety is obtained from three trials. All three trials investigated the triple VX-445 200 mg/tezacaftor 100mg/ivacaftor 150mg morning dose in combination with ivacaftor 150 mg as evening dose.

Study 102 in CF patients 12 years an older is a 24-week, randomized, double-blind, placebo-controlled, parallel-group study in subjects heterozygous for the F508del-CFTR mutation and a minimal function mutation (as defined by the MAH). A total of 403 subjects received at least 1 dose of study drug. Placebo was used as control treatment because no CFTR modulators were approved. The primary

[2] Cystic Fibrosis Foundation. Patient Registry: 2018 Annual Data Report. Bethesda, MD: CysticFibrosisFoundation; 2019.
[3] European Cystic Fibrosis Society. 2017 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2019

endpoint was absolute change from baseline in ppFEV1, which was accompanied by several key secondary endpoints (pulmonary exacerbations, SwCl, CFQ-R RD, BMI).

Study 103 in CF patients 12 years an older is a 4-week, randomized, double-blind, TEZ/IVA-controlled, parallel-group study in subjects homozygous for the F508del-CFTR mutation. A total of 107 subjects received at least 1 dose of study drug. TEZ/IVA (Symkevi) was used a control treatment, as this is an approved therapy in this patient populations. The primary endpoint was absolute change from baseline in ppFEV1, which was accompanied by key secondary endpoints on SwCl and CFQ-R RD score.

Study 105 is an ongoing open-label rollover study that enrolled subjects from study 102 (n=400) and 103 (n=107). This study is designed to support long-term safety (primary) and maintenance of efficacy (secondary). Interim analysis 2 (IA2) is submitted to allow evaluation of long-term safety of patients F/F and F/MF patients. Efficacy data, with an additional 36 week or 24 week treatment, are submitted is for F/F patients which were enrolled in study 103 and for F/MF patients enrolled in study 24, respectively.

The core safety analyses consist of separate analyses of Studies 102 and 103, and the second interim analysis (IA2) of the open-label extension Study 105. The safety profile of VX-445/TEZ/IVA was mainly derived from Study 102. Safety data from Studies 102 and 103 were not pooled because of the substantial differences in the designs of the 2 studies. In addition, analyses of the Cumulative Safety Set and a subset of subjects in the Cumulative Safety Set who received ≥ 48 weeks of treatment with VX-445/TEZ/IVA were submitted.

The Study 102 Safety Set contains all subjects who received at least 1 dose of study drug. The Study 103 Safety includes all subjects who received at least 1 dose of study drug in the Study 103 Treatment Period (i.e., does not include subjects who were only dosed in the TEZ/IVA Run-in Period). The Study 105 Safety Set includes all subjects who received at least 1 dose of study drug in Study 105. The Cumulative Safety Set includes all subjects who received at least 1 dose of VX-445/TEZ/IVA during the parent Studies 102 or 103 and/or during Study 105.

3.2. Favourable effects

Dose regimen
For CF patients 18 years and older with an F/MF mutation three doses (50mg, 100mg and 200mg) of VX-445 were tested in combination with the approved dosage of TEZ/IVA. ppFEV1 and SwCl changes from baseline with the TC are compared to changes from baseline with placebo. A difference in ppFEV1 compared to placebo is seen for all dose tested strengths (11.1, 7.8 and 13.8, for 50, 100 and 200mg respectively). For SwCl, an improvement (decline) compared to placebo is detected (-36.1, -31.0, 36.9 for 50, 100 and 200mg respectively). In all cases, (the efficacy data, the exposure-response models and the simulated efficacy data for FEV1 and SwCl) the 200-mg provides the best performance.

For CF patients 18 years and older with an F/F mutation, only the final 200 mg dose of VX-445 was investigated. A benefit with VX-445/TEZ/IVA compared to TEZ/IVA is seen (ppFEV1:10.6%; SwCl: -40.4 mmol/L).

CF patients 12 years or older with the F/MF genotype (study 102)
Ivacaftor in combination with VX-445/TEZ/IVA showed an absolute change in ppFEV1 through week 24 between the IVA 150 mg and VX-445/TEZ/IVA versus placebo groups of 14.3% (CI 95%: 12.7 – 15.8; p<0.0001) in favour of the triple combination with ivacaftor. A comparable difference was observed at week 4 already (13.7; CI 95% 12.0 - 15.3; p<0.0001). Approximately 80% patients treated with the TC have an increase in ppFEV1 >5%, compared to 15% in the placebo group.

Several key secondary endpoints were analysed. For pulmonary exacerbations, the rate ratio was 0.37 (95% CI: 0.25 – 0.55, p<0.0001) in favour of VX-445/TEZ/IVA in combination with ivacaftor, a reduction of 63%. The hazard ratio for time-to-first pulmonary exacerbations was also in favour of the triple combination (HR: 0.34; 95% CI 0.22, 0.52; p<0.0001). For changes in SwCl from baseline, a stable reduction of -41.8 mmol/L (95% CI: -44.4 to -39.3; p< 0.0001) through week 24 compared to placebo was observed. A higher CRQ-R RD score was observed in the TC arm compared to the placebo arm (20.2 points; 95% CI 17.5,23.0; p<0.0001). All other CFQ-R domains indicated an improvement with the TC compared to placebo. Last, an absolute change of 1.04 (95% CI: 0.85, 1.23; p<0.0001) compared to placebo was seen in BMI.

All other endpoints also showed a positive effect for VX-445/TEZ/IVA compared to placebo.

Consistent and significant benefits in ppFEV1 favouring VX-445/TEZ/IVA in combination with ivacaftor were observed across all prespecified subgroups: age, sex, baseline lung function, region, *P. aeruginosa* infection, and baseline use of common CF medications.

An ad-hoc subgroup analysis was performed on patients included based in genetic criterion 1 (likely to protein translated) and on criterion 2 (missense not responding the TEZ and/or IVA *in vitro*). Class 1 (MF) mutant patients show an absolute change from baseline in ppFEV1 of 14.8% comparing the triple combination with placebo. The missense mutant patients show a difference in ppFEV1 of 12.9%. Further subdivision of these genotypes (nonsense, splicing, and indel-frameshift) and FRT responsiveness show reasonably similar results. Subject treated with the TC in parent study continue to have a comparable benefit at 24 weeks (study 102) and through 48 weeks (study 105) of treatment, respectively (ppFEV1: 13.9 vs 14.3; SwCl: -42.2 vs -49.0; CFQ-R RD: 17.5 vs 20.1). Patients which received placebo in the parent study show similar benefits (ppFEV1: 14.9, SwCL: -50.3, CFQ-R: 19.2) in these parameters after 24 weeks of VX-445/TEZ/IVA treatment in combination with ivacaftor.

With the results from study 105, also data for exacerbations and nutritional status became available. With regard to the number of PEx an estimated event rate per year of 0.32 (95% CI: 0.24-0.44) is anticipated. With regard to the nutritional status, a benefit compared to baseline is observed for all parameters (change in BMI, BMI z-score and body weight).

Real world data from the US CFFPR for F/MF mutations showed consistent results with what was seen in the clinical study 102.

CF patients 12 years or older with the F/F genotype (study 103/105)
VX-445/TEZ/IVA in combination with ivacaftor showed an absolute change in ppFEV1 at week 4 between the VX-445/TEZ/IVA and TEZ/IVA groups of 10.0% (7.4 – 12.6; p<0.0001) in favor of the triple combination. Approximately 70% patients treated with the TC have an increase in ppFEV1 >5%, compared to 13% in the TEZ/IVA group.

For the key secondary endpoint, change in SwCl from baseline, a reduction of -45.1 mmol/L (95% CI: -50.1 to -40.1; p< 0.0001) at week 4 is observed after treatment with VX-445/TEZ/IVA compared to TEZ/IVA. Change in CRQ-R RD score, key secondary endpoint, improved significantly in the TC arm compared to the TEZ/IVA arm (17.4 points; 95% CI 11.8,23.0; p<0.0001), all other CFQ-R domains indicated an improvement with the TC compared to TEZ/IVA.

Ad hoc analyses on BMI and weight also demonstrate of beneficial effect of the TC over TEZ/IVA.

Consistent benefits in ppFEV1 favouring VX-445/TEZ/IVA in combination with ivacaftor were observed across all prespecified subgroups: age, sex, baseline lung function, region, P. aeruginosa infection, and baseline use of common CF medications.

Subject treated with the TC in combination with ivacaftor in parent study continue to have a similar benefit at 4 weeks (study 103) and through 36 (ppFEV1) or 24 weeks (SwCL and CFQ-R) (study 105) of treatment, respectively (ppFEV1: 10.4 vs 11.9; SwCl: -43.4 vs -47.2; CFQ-R RD: 16vs 14.3). Patients which received placebo in the parent study show comparable benefits (ppFEV1: 12.8, SwCL: -49.4, CFQ-R: 13.8) in these parameters after 36/24 weeks of VX-445/TEZ/IVA treatment in combination with ivacaftor.

With regard to the number of PEx an estimated event rate per year of 0.30 (95% CI: 0.20-0.45) and a probability of event-free survival of 0.859 (95% CI: 0.777-0.912) is anticipated. With regard to the nutritional status, a benefit compared to baseline is observed for all parameters (change in BMI, BMI z-score and body weight).

Real world data from the US CFFPR for F/F showed consistent results with what was seen in the clinical study 103.

CF patients 12 years or older with the F/RF and F/G genotype (real world data).

No clinical data was provided for the F/RF and F/G genotypes. Real world data from the US CFFPR for F/RF and F/G patients treated with VX-445/TEZ/IVA were however provided towards the end of the assessment. Based on the available data, improvements in ppFEV1 were seen in the F/G and F/RF populations of 4.3% and 2.7% respectively, compared to a baseline ppFEV1 measurement before the start of VX-445/TEZ/IVA therapy.

3.3. Uncertainties and limitations about favourable effects

The MAH hypothesis that if a modulator has a large effect on the *F508del-CFTR,* the presence of a single *F508del* allele would be sufficient to derive a clinical benefit (as defined by the F/any treatment paradigm) could not be demonstrated unambiguously, as it is theoretically still possible that some of the MF mutants may make a minor contribution to the *CFTR*-mediated chloride transport upon treatment with VX-445/TEZ/IVA in combination with ivacaftor.

CF patients 12 years or older with the F/MF and F/F genotype (study 102 and study 103)
In the F/MF patients, placebo is used as a comparator and in F/F TEZ/IVA are used as comparator. The added benefit over VX-445 monotherapy or VX-445/IVA is not investigated in a clinical setting.

In study 102 the definition of an MF mutation (1) no protein or (2) not responding to TEZ, IVA or TEZ/IVA in vitro) is different when compared to the standard MF definition (Class I, II and III mutations). An ad-hoc subgroup analysis showed a consistent benefit in the patient included based on criterion 1 (and in the nonsense, splicing and indel frameshift subgroups). However, some small uncertainties remain on whether all criterion (1) mutants do not form a protein.

Not all known MF mutations can be tested in clinical trial setting.

CF patients 12 years or older with the F/F genotype (study 103/105)

Stratification according to ppFEV1 was applied on the ppFEV1 measurements taken after at least 13 days of TEZ/IVA run-in, rather than the screening ppFEV1 values. These ppFEV1 measurements are influenced by whether the patients were Vertex CFTR modulator naïve or experienced. The data suggests that the screening period of 4 weeks may not have been sufficient for CFTR-modulator naïve patients randomized to TEZ/IVA to derive the full benefit of this treatment by time of baseline ppFEV1 assessment. Consequently, it is considered that the magnitude of the treatment effect of VX-445/TEZ/IVA vs TEZ/IVA in the overall study 102 population may be overestimated and that the treatment effect estimate obtained in the CFTR-modulator experienced patients is relevant to prescribers (LS mean 7.8%, 95% CI (4.8,10.8)).

Effect on number of PEx can only be determined by data from study 105, without a control group or event rate at baseline present. When comparing the observed PEx data for study 103/105 to the data from for the VX-445/TEZ/IVA group in study 102 these are considered similar. Therefore, the presented exacerbation results for F/F patients from study 105, are likely to be supportive for the benefit seen with the TC.

CF patients 12 years or older with the F/RF and F/G genotype (real world data).

The registry data presented is in itself limited and not sufficiently detailed, and as such raises questions. For example, the exact modulator therapy used, the duration of use is not known, as well as included specific genotypes and individual patient efficacy data not present. Unavailability of such information is inherent to obtaining data from a registry but leads to questioning whether the patients in the analysis set can be considered sufficiently representative of the overall F/G and F/RF populations to draw conclusions on these populations. Bearing in mind the limitations and questions arising from the registry data, the magnitude of the additional response from treatment with VX-445/TEZ/IVA over prior *CFTR* modulator therapies is not overwhelming. It is unexpected that the F/G group had a greater gain than that seen in the F/RF population. Indeed, in view of the limited efficacy observed in clinical trials for F/RF patients treated with TEZ/IVA compared those patients with G/any mutations treated with IVA, it would be considered that F/RF group should have had more potential for improvement with VX-445/TEZ/IVA by treating the F allele.

Overall, due to the uncertainties on the patients included and the effect size seen, these data cannot be accepted as the main data source for the F/G and F/RF populations.

3.4. Unfavourable effects

As most patients were included in Study 102, the safety profile of VX-445/TEZ/IVA in combination with ivacaftor was mainly determined by Study 102.

Treatment-emergent AEs were reported for nearly all patients in both arms in the Study 102 Safety Set (93.1% of patients in the VX-445/TEZ/IVA arm vs. 96.0% in the placebo arm). TEAEs with an incidence of at least 8% in either treatment group and in VX-445/TEZ/IVA >1% higher than in placebo were headache, diarrhoea, upper respiratory tract infection, abdominal pain, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, blood creatine phosphokinase increased, nasal congestion, rash, and rhinorrhoea. Important AEs observed with incidence rates ≥ 3% and ≥1% more frequent than placebo are influenza, wheezing and hypoglycaemia.

The most common adverse reactions experienced by patients aged 12 years and older were headache (17.3%), diarrhoea (12.9%) and upper respiratory tract infection (11.9%). Adverse drug reactions were mostly mild to moderate and resolved without requiring treatment discontinuation.

Related AEs occurred in 5.0% of patients treated with VX-445/TEZ/IVA and in 3.0% treated with placebo; 42.6% of the subject in the VX-445/TEZ/IVA group and 22.9% subjects in the placebo group had an AE assessed by the investigator as possibly related.

Grade 3-4 AEs were reported for 9.4% (VX-445/TEZ/IVA) vs. 7.5% (placebo) of patients; infective pulmonary exacerbation of cystic fibrosis (4.5%, placebo) and blood creatine increased (2%, VX-445/TEZ/IVA), ALT increased (1%, VX-445/TEZ/IVA), and AST increased (1%, VX-445/TEZ/IVA) were the only Grade 3 or 4 AEs that had an incidence of at least 1% in either treatment group.

SAEs were reported for 13.9% (VX-445/TEZ/IVA) vs. 20.9 % (placebo). The SAEs that occurred in ≥ 1% of patients in either treatment group were infective PEx of CF (5.4% vs. 16.4%), haemoptysis (1.0% vs. 1.5%) and rash (1.0% vs. 0.5%) and influenza (1.5% vs 0%). Related SAEs occurred in

3.0% (VX-445/TEZ/IVA) vs. 1.0% (placebo). No related SAEs occurred in 2 or more patients in either treatment group.

Transaminase elevations are common in CF patients receiving IVA monotherapy, TEZ/IVA, and VX-445/TEZ/IVA. In the pivotal VX-445/TEZ/IVA, exclusion criteria for patients with pre-existing liver function impairments were more stringent compared to the Orkambi trials and Symkevi. The incidence of transaminase elevation adverse events was 2-3 times higher in the VX-445/TEZ/IVA group than in the placebo group. The vast majority of the events were non-severe, non-serious and did not lead to treatment discontinuation. Increases from baseline in mean total bilirubin were also observed in the VX-445/TEZ/IVA group, with a greater increase in indirect bilirubin than direct bilirubin, while in the placebo group, changes from baseline in mean total bilirubin were minimal. AEs associated with bilirubin elevation occurred in 10 (5.0%) subjects in the VX-445/TEZ/IVA group and 2 (1.0%) subjects in the placebo group. None of the AEs of bilirubin elevation were serious or led to treatment discontinuation. This is already addressed in the SmPC sections 4.4 and 4.8 of Kalydeco.

Rash occurred more frequently in the VX-445/TEZ/IVA group (10.9%, 22 subjects) than in the placebo group (6.5%, 13 subjects). Most rashes occurred within the first 3 weeks of study drug treatment. Serious rash events occurred in 3 (1.5%) subjects in the VX-445/TEZ/IVA group compared to 1 (0.5%) subject in the placebo group. A warning section 4.4 has been included in the Kalydeco SmPC.

AEs of CK elevation occurred more frequently in subjects in the VX-445/TEZ/IVA group compared to the placebo group. The majority were asymptomatic laboratory elevations, many of which were preceded by exercise. The 2 subjects in the VX-445/TEZ/IVA group with AEs of rhabdomyolysis presented with CK elevations, and neither subject had clinical features of rhabdomyolysis (e.g., kidney involvement, myoglobinuria). Both subjects had performed strenuous exercise. However, the Kalydeco SmPC has been amended to reflect increase in blood creatine phosphokinase.

Incidental increases from baseline in mean BP parameters were observed in the VX-445/TEZ/IVA group. Only a limited number of subjects had a blood pressure in the hypertensive range. However, the Kalydeco SmPC has been amended to reflect increase of blood pressure.

In Study 103 Safety set, the incidence of subjects with at least 1 AE was 58.2% in the VX-445/TEZ/IVA group and 63.5% in the TEZ/IVA group. In general, a similar pattern was in the TEAEs, but overall, with lower frequencies.

The long-term safety data (Study 105 Safety Set, OLS) showed decreased exposure-adjusted event rate of (related AEs), Grade 3-4 AEs, SAEs with VX-445/TEZ/IVA compared to the Study 102 Safety Set. In the Cumulative Safety Set, the safety profile is quite similar to the safety profile of Study 102 Safety Set.

In Study 105 Safety Set, 7 (1.4%) subjects had AEs that led to treatment discontinuation, of whom 3 subjects discontinued due to AEs of transaminase elevation. The other subjects discontinued treatment due to AEs of depression (1 subject), rash (1 subject), tinnitus and contusion (1 subject), and hepatic encephalopathy (1 subject).

Influenza was reported in the clinical studies performed in association with Kaftrio and therefore has been included as an ADR in section 4.8. The applicant committed to continue the monitoring of influenza in the post marketing setting.

3.5. Uncertainties and limitations about unfavourable effects

In Study 105 IA2, 229 subject patients had an exposure of > 24 ≤ 48 weeks and 271 patients had an exposure ≥48 weeks. More information will become available during post-marketing pharmacovigilance when final results of the Study 105 will be submitted.

Ivacaftor in combination with VX-445/TEZ/IVA should not be used in patients with severe hepatic impairment. In addition, only in case of urgent and unavoidable need for treatment with Kaftrio and after weighing the benefits and risks of such treatment, Ivacaftor in combination with VX-445/TEZ/IVA may be used in patients with moderate hepatic impairment applying a dose reduction, this has been introduced in the Kalydeco SmPC.

Rash occurred frequently with Ivacaftor in combination with VX-445/TEZ/IVA treatment. There was an increase in the incidence of rash in female subjects taking hormonal therapy compared with those not taking hormonal therapy; the increase was larger in the Ivacaftor in combination with VX-445/TEZ/IVA group than in the placebo group. Therefore, a role for hormonal therapy in the occurrence of rash cannot be excluded. A warning in section 4.4. of the SmPC has been included.

3.6. Effects Table

Table 43. Effects Table for Kalydeco in a combination regimen with Kaftrio for the treatment of patients aged 12 years and older who have at least one F508del mutation in the CFTR gene (data cut-off: 31 October 2019 (study 102, 103 and 105))

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref. **
Favourable Effects						
CF patients with the F/MF genotype						
			VX/TEZ/IVA	**Placebo**		
ppFEV1	Change 0-24 wks LSM(95% CI)	%	13.9 (12.8, 15.0)	-0.4 (-1.5, 0.7)	**SoE**: 14.3 (12.7, 15.8) p<.0001 Highly clinically relevant	1
CFQ-R RD	Change 0-24 wks LSM(95% CI)	points	17.5 (15.6, 19.5)	-2.7 (-4.6, -0.8)	**SoE:** 20.2(17.5, 23.0) p<.0001	1
PEx	Event rate 0-24 wks	Number/yr	0.37	0.98	**SoE:** 0.37 (0.25, 0.55) p<.0001	1
BMI	Change 0-24 wks LSM(95% CI)	Kg/m^2	1.13 (0.99, 1.26)	0.09 (-0.05, 0.22)	**SoE:** 1.04 (0.85, 1.23) p<.0001	1
Sweat Chloride	Change 0-24 wks LSM(95% CI)	mmol/L	-42.2 (-44.0, -40.4)	-0.4 (-2.2, 1.4)	**SoE:** -41.8(-44.4,-39.3) p<.0001	1
CF patients with the F/F genotype						
			VX/TEZ/IVA	**TEZ/IVA**		
ppFEV1	Change 0-4 wks LSM(95% CI)	%	10.4 (8.6, 12.2)	0.4 (-1.4, 2.3)	**SoE:** 10.0 (7.4, 12.6) p<.0001 Highly clinically relevant, confirmed with LT data (24wks) **Unc:** uncontrolled LT results	2/3
CFQ-R RD	Change 0-4 wks LSM(95% CI)	Points	16.0 (12.1, 19.9)	-1.4 (-5.4, 2.6)	**SoE:** 17.4 (11.8, 23.0) p<.0001 Confirmed with LT data (24wks) **Unc:** uncontrolled LT results	2/3
Sweat Chloride	Change 0-4 wks LSM(95% CI))	mmol/L	-43.3 (-46.9, -40.0)	1.7 (-1.9, 5.3)	**SoE:** -45.1(-50.1,-40.1) p<.0001 Confirmed with LT data (24wks) **Unc:** uncontrolled results	2/3
Pulmonary exacerbations	Event rate 0-24 wks	Number/ year	0.30		**Unc**: No comparator arm	2/3
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref. **
Headache		%	17.3	14.9	**Unc**: Limited size of the data set **SoE**: No differences between adults and adolescents	1
Diarrhoea		%	12.9	7.0		1
Abdominal pain		%	9.9	6.0		1
ALT	ALT increased	%	9.9	3.5	Determined based on safety profile of TEZ and IVA (ALT, AST), in combination with pharmacokinetic profile (bilirubine)	1
AST	AST increased	%	9.4	2.0		1
Bilirubine	Bilirubine increased	%	5.0	1.0		1
Blood creatine phosphokinase	Blood creatine phosphokinase increase	%	9.4	4.5		1
Nasal congestion		%	9.4	7.5	**Unc**: Limited size of the data set **SoE**: No differences between adults and adolescents	1
Rash	Rash	%	8.9	4.5		
Rhinorrhoea		%	8.4	3.0		
Rhinitis		%	7.4	5.5		
Influenza		%	6.9	1.5		
Sinusitis		%	5.4	4.0		
Flatulence		%	4.5	1.5		
Hypoglycaemia		%	4.5	1.0		
Respiration abnormal		%	4.5	2.0		
Viral URTI		%	4.5	2.0		
Acne		%	3.5	1.5		
Dizziness		%	3.5	2.5		
Pharyngitis		%	3.0	1.0		
Wheezing		%	3.0	1.0		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref. **
Grade 3-4 TEAEs		%	9.4	7.5		

Abbreviations: URTI upper respiratory tract infection, VX/TEZ/IVA VX-445 +Tezacaftor +Ivacaftor, PE Pulmonary Exacerbations
**1 refers to study 102, 2 refers to study 103 and 3 refers to study 105.
Notes: the safety profile in Study 103 Safety Set, and Study 103 Safety Set is generally comparable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

According to the MAH, if a modulator has a large effect on the *F508del-CFTR*, then the presence of a single F508del allele would be sufficient to derive a clinical benefit. Based on this new hypothesis and the results from study 102 and 103, a broad indication was initially proposed to include all patients with at least one *F508del* mutation independently of the second allele. This means that efficacy for non-tested populations of F/MF, F/RF and F/G should be extrapolated. It should be noted that uncertainties remain on the value of the new paradigm proposed, as it is not accepted by CHMP that all class 1 MF mutations are equal, and that no protein is produced in each and every case. Therefore, it cannot be excluded that some of the MF mutants may make a contribution to the *CFTR*-mediated chloride transport upon treatment with Ivacaftor in combination with VX-445/TEZ/IVA.

CF patients 12 years or older with the F/MF genotype

Importance of the favourable effects
The observed difference of 14.3% between Ivacaftor in combination with VX-445/TEZ/IVA and placebo in absolute change of ppFEV1 is well above the predefined threshold (5%) and also above the definition of clinical relevance in the context of the natural decline in CF patients in the pivotal study 102. Approximately 80% patients treated with the TC have a benefit of ppFEV1 >5%, compared to 15% in the placebo group. The results are considered clinically relevant.

The rate ratio of 0.37 for exacerbations comparing VX-445/TEZ/IVA to placebo is relevant.

Strength of the evidence
Consistent improvements in ppFEV1 favouring Ivacaftor in combination with VX-445/TEZ/IVA were observed across all prespecified subgroups.

The results of the primary parameter are supported by all key secondary parameters. CFQ-R respiratory domain, BMI and sweat chloride all showed improvements well above the MCID.

The results were consistent across the subgroups of criterion 1 and criterion 2 mutations and upon further subdivision based on genotype or *in vitro* responsiveness.

Impact of the uncertainties

Not all known MF mutations can be tested in a clinical trial. The clinical benefit seen in these F/MF patients has such a large effect size, that it is unlikely that uncertainties related to MF mutations not being tested, the absence of a direct in vitro in vivo comparison, inclusion criteria or chosen dose regimen will affect the data to such an extent that the benefit could be questioned.

Based on the pre-clinical data, the clinical data and the lack of evidence that all MF mutation do not form a protein, the F508del-only treatment paradigm has not been definitively substantiated.

The consistent results in the F/MF population subgroups, together with the magnitude of the efficacy observed indicate that extrapolation to untested MF mutations can however be accepted.

CF patients 12 years or older with the F/F genotype

Importance of the favourable effects
The observed difference of 10.0% between VX-445/TEZ/IVA and TEZ/IVA in absolute change of ppFEV1 is well above the predefined threshold (5%) and also above the definition of clinical relevance

in the context of the natural decline in CF patients in the pivotal study 103. Approximately 70% patients treated with the TC have a benefit of ppFEV1 >5%, compared to 13% in the TEZ/IVA group. The results are considered clinically relevant.

The results from study 105 confirm the benefit in FEV1 was maintained until 24 week. For pulmonary exacerbations, the estimated event rate per year was 0.30 in the F/F population of study 105.

Strength of the evidence
Consistent improvements in ppFEV1 favouring Ivacaftor in combination with VX-445/TEZ/IVA were observed across all prespecified subgroups.

The result of the primary parameter is supported by all key secondary parameters. CFQ-R respiratory domain, BMI and sweat chloride all showed improvements well above the MCID.

Study 103 had a duration of only 4 weeks, but from study 105 it was concluded that all effect seen in primary and secondary endpoints at week 4 were maintained through week 24.

Impact of the uncertainties
The clinical benefit seen in these patients has such a large effect size, that it is unlikely that uncertainties related to for example sensitivity analyses, inclusion criteria or chosen dose regimen will affect the data in such an extent that this benefit could be questioned.

While there are no controlled data after 4 weeks for F/F patients due to the short study treatment duration, limited open label extension data from the 107 patients (F/F) that enrolled from parent Study 103 are provided. For the key parameters such as ppFEV1, Sweat Chloride, CFQ-R as well as rate of pulmonary exacerbations the improvements seen at 4 weeks appear to be sustained in all patients, and the BMI, BMI z score and weight outcomes seem to continue to improve. The requested ongoing results from F/F patients in Study 105 remain favourable. Therefore, the limitation of the short-controlled treatment period can be accepted.

CF patients with the 12 years or older F/RF or F/G genotype

Kalydeco monotherapy has been shown to result in an improvement in ppFEV1 for F/G subjects while the improvement in the case of F/RF with Symkevi (which excludes the most prevalent RF mutation, i.e., *R117H*) is more limited. Thus, there is still a need for better treatment for these patients.

In the current variation no *in vitro* data have been presented, either in Fisher Rat Typhoid (FRT) cells (a heterologous system which allows the expression of a single CFTR mutant) or in Human Bronchial Epithelial (HBE) cells from donors with CF. No clinical data have been submitted either to assess the benefit risk in patients with F/G and F/RF mutations. Real world data form the US registry were provided. The ppFEV1 results suggest improvement on top of other *CFTR* modulators, but registry data come with many uncertainties due to bias and missing information.

Cross-study comparison, responder analysis and the registry data on its own without the ongoing clinical study 104 data in F/G and F/RF mutations do not sufficiently support the added benefit of VX445/TEZ/IVA over approved modulator therapies. The lack of clear demonstration of the alleged "new paradigm" (F/any) does not support the extrapolation of the available data to these populations. Demonstration of clinical efficacy and safety by a randomized controlled trial is thus needed. Therefore, the CHMP considered that the efficacy has been demonstrated only in patients with F/F and F/MF mutations where randomized clinical trial data are available.

Study 104, performed in this population, is ongoing. Results from this study will be submitted by the MAH in a variation procedure as soon as available, in order to help estimate the magnitude of additional benefit to these patients.

Safety

Ivacaftor in combination with VX-445/TEZ/IVA was well tolerated with low discontinuation rates due to AEs. The safety profile of the combination is recognizable when compared with the already licensed components and appeared comparable across studies. However, there were more adverse events for increased ALT, AST and bilirubin indicative for hepatic involvement. Based on a PK study in subjects with moderate hepatic impairment, yielding increased exposure to VX-445, Ivacaftor in combination with VX-445/TEZ/IVA is not recommended in patients with moderate hepatic impairment. Only in case of urgent and unavoidable need for treatment with Ivacaftor in combination with Kaftrio and after weighing the benefits and risks of such treatment, Ivacaftor in combination with VX-445/TEZ/IVA may be used in patients with moderate hepatic impairment applying a dose reduction. Expected exposure in patients with severe hepatic impairment has not been investigated but is expected to be higher than that in patients with moderate hepatic impairment, and therefore, in the absence of further data in this patient population, Ivacaftor in combination with VX-445/TEZ/IVA should not be used in such patients.

3.7.2. Balance of benefits and risks

The balance of benefits and risks has to be determined in three separate populations: the patients for whom preclinical and or clinical data is available (F/F and tested F/MF) and for the broader set of patients 12 years and older who have at least one *F508del* mutation in the CFTR gene.

For CF patients with the F/F genotype, the placebo-controlled study provided efficacy data that demonstrate that ivacaftor in combination with VX-445/TEZ/IVA provides a clinical benefit, both in the primary and the key secondary endpoints.

For CF patients with the F/MF genotype included in study 102, the active (TEZ/IVA) control study also provided efficacy data that demonstrate that ivacaftor in combination with VX-445/TEZ/IVA provides a clinical benefit, both in the primary and the key secondary endpoints.

For both populations, the results were considered sufficiently robust and clinically relevant.

The safety profile of ivacaftor in combination with VX-445/TEZ/IVA was derived primarily from Study 102. The extensive clinical experiences with CFTR modulator therapies (including IVA and TEZ/IVA) indicate that the safety profile is consistent across different genotypes for each of the individual CFTR modulator treatments. As such, the safety profile established from Study 102 in F/MF subjects is considered representative for the entire proposed indication, which is supported by the comparable safety profile observed in Study 103.

Overall, ivacaftor in combination with VX-445/TEZ/IVA was well tolerated with low discontinuation rates due to AEs. Most important adverse events concerned the adverse events indicative for hepatic involvement (ALT, AST and bilirubin). At the moment until more data become available, ivacaftor in combination with VX-445/TEZ/IVA may be used in patients with moderate hepatic impairment applying a dose reduction. only in case of urgent and unavoidable need for treatment with ivacaftor in combination with Kaftrio and after weighing the benefits and risks of such treatment, ivacaftor in combination with VX-445/TEZ/IVA may be used in patients with moderate hepatic impairment applying a dose reduction.

The long-term study 105 revealed no important additional safety events.

Overall, the data of clinical studies 102, 105 and 103 indicate a large clinical benefit of ivacaftor in combination with VX-445/TEX/IVA in F/F and F/MF patients. Although the evidence for the *F508de*l-only hypothesis is considered not definitively conclusive and some uncertainties remain, the highly clinically relevant benefit, and the consistency of these effects seen with ivacaftor in combination with

VX-445/TEZ/IVA in studies/subgroups make the extrapolation to all patients with an F/MF genotype acceptable.

For F/RF and F/G population, the evidence for the F508del-only hypothesis is considered not definitively conclusive. The registry data provided for these patients are welcome, but subject to limitations and to bias to reliably demonstrate the efficacy and safety of ivacaftor in combination with VX445/TEZ/IVA in F/G and F/RF patients. In conclusion the CHMP was of the view that the registry data do not obviate the need for robust, comparative, clinical data in F/G and F/RF patients from clinical trials.

While the benefit/risk balance for the extension of the indication to the broad population (i.e., all CF patients who have at least one *F508del* mutation) is considered negative, a positive B/R balance can be considered for the F/F and F/MF patient populations

The indication granted by CHMP for Kalydeco tablets is therefore as follows:

- In a combination regimen with ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets for the treatment of adults and adolescents aged 12 years and older with CF who are homozygous for *F508del* mutation in the *CFTR* gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation (see section 5.1).

3.8. Conclusions

The overall B/R of Kalydeco is positive in a combination regimen with ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis who are homozygous for *F508del* mutation in the CFTR gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the combination regimen of the ivacaftor 150 mg tablets with elexacaftor/tezacaftor/ivacaftor fixed dose combination (FDC) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis who who are homozygous for *F508del* mutation in the *CFTR* gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to version 8.8.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Kalydeco is not similar to Symkevi, TOBI Podhaler, Bronchitol and Kaftrio (CHMP opinion 10 July 2020, currently pending EC Commission Decision (CD)) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0091/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Kalydeco-H-C-002494-II-0085'.